IPHA Submission on HIQA's Consultation on smoking cessation

03rd Feb 2017

GENERAL

The Irish **Pharmaceutical Healthcare** Association (IPHA) represents the international research-based companies who are responsible for developing, manufacturing and bringing innovative medicines to the Irish market.

We support the need for evidence based decision making, welcome the principle of a review of smoking cessation methods and applaud the government's efforts to prevent and reduce the use of tobacco. We support the continued availability of treatments that are **scientifically proven** as being effective in reducing and preventing tobacco use.

However, IPHA has serious concerns at the way in which e-cigarettes are portrayed in this Health Technology Assessment (HTA) report and were portrayed in the press release to its publication. E-cigarettes are not regulated as medicines, have no robust safety and efficacy data, and cannot make any health claims about reducing and preventing the use of tobacco. Under the 2014 EU Tobacco Products Directive (TPD), these products are regulated as "tobacco related products" and forbidden from making any type of health claims. Moreover they are prohibited from sales in pharmacies by our national regulator, prohibited from making smoking cessation claims by the FDA not recognized by the World Health Organization (WHO) as a product to reduce tobacco use are owned primarily by tobacco companies (according to WHO) and which are rapidly being adopted by children.

BACKGROUND

IPHA seeks to collaborate with governments, regulatory authorities and healthcare organizations to establish and promote policies and guidelines that improve public health whilst reducing the negative impacts of ongoing tobacco use. We particularly support those policies and guidelines that encourage wider access to proven smoking cessation services and therapies. We also support consumer access to, choice of, and information about the variety of healthcare products and services that have scientifically proven safety and efficacy in helping to reduce and stop the use of tobacco.

We appreciate that HIQA may have included e-cigarettes in its HTA in order to reflect what is happening in the market and to future proof its guidance, despite it not having been explicit that they would be considered as smoking cessation therapies/interventions within the

original terms of reference. However, we find that the degree of emphasis and weight that has been given to e-cigarette throughout the guidance and the fact that e-cigarettes were considered equally alongside established, licensed pharmaceutical smoking cessation aids with robust evidence of efficacy and safety for the purposes of this review to be of serious concern.

IPHA has serious concerns about the way in which e-cigarettes are treated within the HIQA HTA, because of the following non-exhaustive list of issues around e-cigarettes:

- There are no e-cigarettes licensed as smoking cessation aids in Ireland
- The is a worrying lack of evidence on the efficacy or long-term safety of e-cigarettes
- The **regulator of pharmacies and pharmacists in Ireland,** the Pharmaceutical Society of Ireland (PSI), **does not permit e-cigarettes to be sold in pharmacies** in Ireland as to do so would infer, incorrectly, that their safety and efficacy had been assesses and can be assured.
- The **WHO** advises that unless e-cigarettes are deemed safe and effective in reducing and stopping smoking and become of acceptable quality, **governments should prohibit** manufacturers and third parties from making health claims for e-cigarettes, including that they are smoking cessation aids.
- A systematic review on the use of e-cigarettes for smoking cessation by one of the most well respected internationally acclaimed review bodies (Cochrane[1]) graded the quality of the two randomised controlled **e-cigarette studies referred to in the HIQA report as "low" and "very low**".
- E-cigarettes **are not recommended by the HSE** as a means of smoking cessation on the grounds that *"the Health Service can only endorse products that are proven to be safe, and proven to be effective; e-cigarettes have not yet achieved either test."*
- The relevant legislation requires that any e-cigarette presented for smoking cessation[2] should be regulated as a medicinal product and the competent authority responsible for overseeing the implementation of Article 20 of the revised 2014 EU TPD in Ireland would be **required to intervene** should an e-cigarette manufacturer present or promote their product as a medicinal product unless it was a licensed as a medicine. Under that law e-cigarettes are classified as "tobacco-related products", forbidden from health claims on any impact on reducing and preventing smoking and must carry significant health warnings. Any and all products that have scientifically proven safety and efficacy should be classified as medicines and subject to national and international law.

[1] The Cochrane review is a well-respected, internationally acclaimed review and its evidence should be give due weight, which is not evidenced in the HIQA HTA (page 134, line 8-9) etc. These Cochrane reviews are systematic reviews of primary research in human health care and health policy and are internationally recognized as the **highest standard** in evidence-based health care resources.

[2] The revised EU TPD (2014/40/EU), which entered into force on 19.05.14 and became applicable in the EU Member States on 20.05.16, requires that any e-cigarette presented as a medicinal product (i.e. for smoking cessation or tobacco/nicotine dependence) should be regulated as a medicinal product for human use under the auspices of Directive 2001/83/EC.

SUMMARY

We support the need for evidence based decision making including the principle of a review of smoking cessation methods, and proportionate solutions to ensure that Ireland's citizens have the greatest access to scientifically proven safe and effective treatments to help reduce and prevent tobacco use.

The current draft report, and associated press release strongly, and against international evidence, infers the efficacy and safety of e-cigarettes. The regulator of pharmacy in Ireland (PSI), WHO, FDA, Cochrane review etc. all have serious concerns about e-cigarettes, which are unregulated devices. We strongly recommend that the HIQA report is amended to give due weight to evidence to scientifically-proven therapies and remove the unwarranted endorsement of e-cigarettes, which have no clinical evidence of safety and efficacy in reducing tobacco use, do not use internationally-recognized good manufacturing and quality standards, are not licenced as smoking cessation aids, are a serious potential health risk, are owned primarily by tobacco companies and which are rapidly being adopted by children. Current e-cigarette use among US high school students has increased from 1.5% in 2011 to 16% in 2015 (> 900% increase).

The safety and efficacy of NRT for smoking cessation has been long established as confirmed by, amongst others, the Cochrane Collaboration and the National Institute for Health and Care Excellence (NICE) in England, The WHO has also listed both NRT patch and gum in their Model List of Essential Medicines and their use is endorsed in the WHO Implementation Guideline for Article 14 of the WHO Framework Convention on Tobacco Control. Importantly, in the Irish context, the National Standard for Tobacco Cessation Support Programme published by the HSE also recommends the use of NRT.

SPECIFIC CONCERNS

In IPHA's opinion the overall conclusion and tone of the HIQA report in relation to e-cigarettes is not appropriate for a product whose dangers not only include the toxins that they emanate, but also their lack of safety data and their ability to encourage smoking commencement in the general population.

E-cigarettes are unregulated devices that the PSI has advised should not be sold in pharmacies. This is because selling them in a pharmacy would infer that their safety and efficacy has been assessed and can be assured. In fact, neither their efficacy nor their safety can be assured unless they are classified and regulated as medicinal products with scientifically-based evidence of safety and efficacy, and thus the PSI, the national regulator of pharmacies and pharmacists, does not permit their sale or display in pharmacies.

Additionally, the WHO has collected international evidence on this topic confirms that e-cigarettes are now owned primarily by tobacco companies[3]. The WHO report indicates that

[3] The 2012 WHO report advises as follows: *The ENDS market, initially dominated by companies with no links to the tobacco industry, **is increasingly owned by the tobacco industry**. All main transnational tobacco companies sell ENDS and one of them is launching legal proceedings over patents against its rivals as they become increasingly aggressive in the battle for the fast-growing e-cigarette market. The increasing concentration of the ENDS market in the hands of the **transnational tobacco companies is of grave concern** in light of the history of the corporations that dominate that industry'…Most ENDS products have not been tested by independent scientists but the **limited testing has revealed wide variations in the nature of the toxicity of contents and emissions.***

there is little evidence of safety and on the contrary the WHO advises that the toxins in e-cigarettes are similar to those of smoking.

Furthermore, these devices are appealing to children. A survey supported by the United States Food and Drug Agency and the Centers for Disease Control and Prevention showed that, over the past decade, there has been a significant drop in the use of traditional cigarettes among young people but their use of other tobacco products is rising. Current e-cigarette use among US high school students has increased from 1.5% in 2011 to 16% in 2015 (> 900% increase).

It is generally understood and even detailed in the HIQA report itself that *'If e-cigarette use becomes socially acceptable, it could lead to new use of nicotine by people who have never smoked before, later migration to tobacco cigarettes, long-term nicotine dependency, and other potential as yet unknown harms.'*

- The HIQA report states on page 105 that:

  > *The 10 interventions in the network of pharmacological treatments were analysed in terms of their likely ranking (from best treatment to worst treatment) (Figure 4.5)…E-cigarettes and cytosine both had wide ranges of potential rankings,* ***highlighting the uncertainty in relation to their effectiveness****.*

- The HIQA report states on page 134 that

  > *The Cochrane review of e-cigarettes for smoking cessation described the level of evidence as* ***low.***
  >
  > However, the Cochrane review is a well-respected, internationally acclaimed review and its evidence should be given due weight, which is not evidenced in the HIQA report (page 134, line 8-9 etc). "Low" by GRADE standards indicates that further research is very likely to have an important impact on confidence in the effect estimate, and is likely to change the estimate itself. Thus, we consider the efficacy of e-cigarettes to be largely uncharacterized. In contrast, NRT treatments have been studied in over 100 clinical trials involving tens of thousands of smokers, and have been proven effective in reducing smoking rates and improving quit rates.

- The EU Smoking Cessation Guideline (page 124 extracted below) is quite different to HIQA's approach:

4.2.7 E-cigarettes

E-cigarettes are a new product which are being marketed more frequently and which are presented both as a tobacco replacement product and as a smoking cessation product. Most sales of cartridges for e-cigarettes contain nicotine at various undefined levels. The smoke-like vapour produced by ethylene glycol or glycerol is an irritant when exposure is repeated, but is not a severe toxin in short-term use.

With disposable cartridges, e-cigarette have become more economical than regular cigarettes per nicotine puff absorbed and experimentation with e-cigarettes by young people is becoming more and more common throughout Europe. The e-cigarette has now become a tobacco initiation product, a product for consumption in non-smoking areas, a product to promote smoking. However, it is also presented as a smoking cessation or harm reduction product.

The lack of reliable studies had led most national authorities to prohibit the promotion of this product as a smoking cessation product. Currently, there is no clear-cut response by doctors with regard to this ambiguous product. There is no evidence of frequent or severe adverse effects, but there is likewise no evidence of efficacy for smoking cessation, so in view of the absence of studies health professionals should not recommended this product, but there is no strong argue to contradict a patient's choice if the patient chooses to use e-cigarettes as an adjuvant to other smoking cessation articles.

Emissions of total suspended particulate matter (TSP) derived from e-cigarettes are around 60 mcg/ m^3, 10-15 times lower than those of conventional cigarettes For each of the different fractions of PM, (PM_{1}, $_{2.5}$, $_{7}$, $_{10}$), there is a lower density (ranging from 6 to 21 times) for e-cigarettes compared to conventional cigarettes, but the levels still slightly exceed WHO outdoor air quality guideline values[1].

E-cigarettes were found to have immediate adverse physiologic effects after short-term use that are similar to some of the effects seen with tobacco smoking; however, the long-term health effects of e-cigarette use are unknown but potentially adverse and worthy of further investigation[2].

We believe that the importance of the aforementioned bulleted facts were not given due consideration and in some cases no consideration in the report and particularly in the conclusion. The HIQA Corporate Plan specifically advises that HIQA has statutory responsibility for *'Providing advice that enables the best outcome for people who use our health service and the best use of resources by evaluating the clinical effectiveness and cost-effectiveness of drugs, equipment, diagnostic techniques and health promotion and protection activities'.* We believe that the tone of the conclusion of the current HIQA report, and elements of the content, do not enable the best outcome for patients as it does not provide enough prominence to the WHO, PSI and EU Smoking Cessation Guideline concerns about e-cigarettes nor the body of evidence to support Nicotine Replacement Therapy (NRT) or varenicline.

We therefore, suggest the following changes to the report:

PROPOSED CHANGES

- The HIQA report states on page 101 that:

  The data on e-cigarettes is less clear, influenced by the small number of studies and comparisons available. Relative to control there was statistically significant treatment

effect, although the confidence bounds were wide. Relative to NRT monotherapy there was a small, but not statistically significant treatment benefit.

IPHA proposes that HIQA change this to the following more accurate statement that is in line with the WHO etc.:

The data on e-cigarettes is less clear, influenced by the small number of studies and comparisons available. ~~Relative to control there was statistically significant treatment effect, although the confidence bounds were wide.~~ Relative to NRT monotherapy there was ~~a small, but not~~ no statistically significant treatment benefit.

- The HIQA report states on page 134 that:

  *The Cochrane review of e-cigarettes for smoking cessation described the level of evidence as **low.***

  IPHA proposes that HIQA change this to the following more accurate statement that reflects the standing of the Cochrane review:

  The Cochrane review of e-cigarettes for smoking cessation described the level of evidence as **low.** However, the Cochrane review is a well-respected, internationally acclaimed review. "Low" by GRADE standards indicates that further research is very likely to have an important impact on confidence in the effect estimate, and is likely to change the estimate itself. Thus, we consider the efficacy of e-cigarettes to be largely uncharacterized. In contrast, NRT treatments have been studied in over 100 clinical trials involving tens of thousands of smokers, and have been proven effective in reducing smoking rates and improving quit rates.

- Under 'wider implications' the HIQA report comments as follows:

  If e-cigarette use becomes socially acceptable, it could lead to new use of nicotine by people who have never smoked before, later migration to tobacco cigarettes, long-term nicotine dependency, and other potential as yet unknown harms.

  However, on page 20 under 'safety' the HIQA report states that:

  Safety data on e-cigarettes is limited to two small short-term clinical trials. Mild, temporary adverse drug reactions were found, such as throat and respiratory irritation and dry cough. Toxicological studies have demonstrated that while toxic chemicals may be present in e-cigarette vapour, they are at a lower concentration than in cigarette smoke. E-cigarettes have only been in use for a short time, and so data on long-term toxicity is not yet available. While the clinical effect of long-term e-cigarette use is unknown, the risk to bystanders from 'passive vaping' appears to be very low. The safety of e-cigarettes is

an evolving area of research; while believed to be safer than smoking, evidence on long-term safety has yet to be established.

Therefore, IPHA proposes that HIQA modify page 20 to the following more accurate statement that is in line with international opinion:

Safety data on e-cigarettes is limited to two small short-term clinical trials. Mild, temporary adverse drug reactions were found, such as throat and respiratory irritation and dry cough. ~~Toxicological studies have demonstrated that while toxic chemicals may be present in e-cigarette vapour, they are at a lower concentration than in cigarette smoke.~~ E-cigarettes were found to have immediate adverse physiologic effects after short-term use that are similar to some of the effect seen with tobacco smoking[4]. E-cigarettes are not regulated as medicines, have no robust safety and efficacy data, and cannot make any health claims about reducing and preventing use of tobacco. Under the 2014 EU TPD, these products are regulated as "tobacco related products" and forbidden from making any type of health claims. Moreover they are prohibited from sales in pharmacies by our national regulator and not recognized by the World Health Organization as a recognized product to reduce tobacco use. They are noted by the FDA as being rapidly adopted by young people[5]. If e-cigarette use becomes socially acceptable, it could lead to increased uptake of nicotine products by people who have never smoked before, later migration to tobacco cigarettes, long-term nicotine dependency, and other potential as yet unknown harms. Therefore, the use and normalisation of these products should not be encouraged. While the clinical effect of long-term e-cigarette use is unknown, the risk to bystanders from 'passive vaping' is also unknown and may be substantial ~~appears to be very low~~. The safety of e-cigarettes is an evolving area of research and ~~while believed to be safer than smoking,~~ evidence on long-term safety has yet to be established. Most e-cigarettes have not been tested by independent scientists but the limited testing that has been carried out has revealed wide variations in the nature of the toxicity of contents and emissions[6].

- On Page 21 under 'economic evaluation' the HIQA report states that:

A comparison of alternatives to the current mix of smoking cessation interventions used in Ireland was carried out using international data as an indicator of plausible changes in the usage of the most cost-effective cessation interventions. This included a scenario where combination varenicline and NRT use was maximised, and a scenario where e-cigarette uptake reached levels recently reported in England. This analysis found that maximising the uptake of varenicline and NRT in combination is the most cost-effective strategy. However, it is unclear to what extent policy initiatives can influence overall smoking cessation preferences, particularly in light of the high use of e-cigarettes in Ireland in the

[4]Page 63 of the EU Smoking Cessation Guideline produced by the European Network for Smoking & Tobacco Prevention.
[5] US FDA: Young people are rapidly adopting e-cigarettes, however, young people who use e-cigarettes are heavier (not lighter) smokers. E-cigarette use among high school students has increased from 1.5% in 2011 to 16% in 2015 (> 900% increase). E-cigarettes contain candy flavours (e.g., cherry, chocolate, Turkish delight).
[6] WHO report

absence of any explicit endorsement by quit services. Based on the currently available evidence, an increase in the uptake of e-cigarettes to rates of 45% currently reported in England is likely to improve the cost-effectiveness of the overall mix of cessation interventions in Ireland, by increasing the number of successful quit attempts, again at an acceptable cost.

At this time the use of varenicline and NRT in combination is not supported by the labelling of either varenicline or NRT. The off-label nature of this combination means that there is no recognised posology or safety record on which to make treatment recommendations and therefore they should not be included in the cost effectiveness analysis for use in combination. A statement that they are "best value for money" as a smoking cessation intervention constitutes a tacit recommendation, and implies an established, accepted benefit versus risk assessment in this indication when that is not supported by evidence at this time, nor is it supported by present product labelling. Additionally, without established efficacy or safety, and given the HSE does not advocate their use in combination for smoking cessation, a cost-effectiveness analysis and implied recommendation is not justified.

Therefore, IPHA proposes that HIQA should modify page 21 as follows to remove any inference that HIQA is promoting the off label use of medicines.

A comparison of alternatives to the current mix of smoking cessation interventions used in Ireland was carried out using international data as an indicator of plausible changes in the usage of the most cost-effective cessation interventions. This included a scenario where combination varenicline and NRT use was maximised, and a scenario where e-cigarette uptake reached levels recently reported in England. ~~This~~ While this analysis found that maximising the uptake of varenicline and NRT in combination is the most cost-effective strategy the safety of such off label use of these medicines has not been assessed and therefore cannot be endorsed. ~~However, it~~ It is unclear to what extent policy initiatives can influence overall smoking cessation preferences, particularly in light of the high use of e-cigarettes in Ireland in the absence of any explicit endorsement by quit services. Based on the currently available evidence, an increase in the uptake of e-cigarettes to rates of 45% currently reported in England ~~is likely to improve the cost-effectiveness of the overall mix of cessation interventions in Ireland, by increasing the number of successful quit attempts, again at an acceptable cost~~ suggests that e-cigarettes could become socially acceptable. However, if e-cigarette use becomes socially acceptable, it could lead to increased uptake of nicotine products by people who have never smoked before, later migration to tobacco cigarettes, long-term nicotine dependency, and other potential as yet unknown harms from devices that are not regulated, are not manufactured under GMP and cannot be sold in pharmacies due to the lack of evidence demonstrating their safety and efficacy.

- Page 22 of the HIQA report states that:

The government has an ethical duty to ensure that the media portrayal of the product is appropriately aligned with its known degree of risk. This is dealt with in the recent EU TPD,

which aims to harmonise the quality and safety requirements of tobacco products and e-cigarettes for the benefit of consumers. ***Although negative health effects from the use of e-cigarettes are currently unknown, there is concern that potential legal liability may be possible if future research finds that negative effects do result from their use. Provided appropriate warnings and information leaflets containing accurate information are included with the sale of any such product, it is difficult to see how a legal action might successfully be taken if this were to occur…***

IPHA is of the opinion that the tone of the report is biased towards the use of e-cigarettes and this bias is not supported by available evidence. E-cigarettes are not regulated as medicines, have no robust safety and efficacy data, and cannot make any health claims about reducing and preventing use of tobacco. The safety of the inhalation of glycerine and propylene glycol, contained in e-cigarettes, is not well established other than when heated and oxidised propylene glycol can form propylene oxide, which is a known carcinogen. Under the 2014 EU TPD, these products are regulated as "tobacco related products" and forbidden from making any type of health claims. Moreover they are prohibited from sales in pharmacies by our national regulator and not recognized by the World Health Organization as a recognized product to reduce tobacco use. They are noted by the FDA as being rapidly adopted by young people[7].If e-cigarette use becomes socially acceptable, it could lead to increased uptake of nicotine products by people who have never smoked before, later migration to tobacco cigarettes, long-term nicotine dependency, and other potential as yet unknown harms. Therefore, the use and normalisation of these products should not be encouraged.

E-cigarettes cannot be presented as smoking cessation aids unless they are classified as medicinal products, subject to Irish pharmaceutical laws and standards, and such products would be required to be the subject of a marketing authorisation before being placed on the market in Ireland.

Furthermore, the position of the PSI is that it would not be appropriate for any of these products to be offered for sale or supply in retail pharmacy businesses in Ireland. Members of the public have a right to expect that the quality, safety and efficacy of any products supplied in pharmacies have been appropriately established and independently assured. As detailed in the PSI position paper on e-cigarettes, pharmacists are required to ensure that products supplied to patients do not pose a hazard to a patient's health or wellbeing, as may be the case if a person were to resort to a particular product in respect of which the safety and efficacy had not been established against other products and treatments that have met the required standards of safety and efficacy.

Only products with demonstrated safety and efficacy of reducing and stopping smoking should be registered as medicinal products and be allowed to make smoking cessation claims. However, in contrast to the WHO recommendation the HIQA report appears to be endorsing e-cigarettes.

[7] US FDA: Young people are rapidly adopting e-cigarettes, however, young people who use e-cigarettes are heavier (not lighter) smokers. E-cigarette use among high school students has increased from 1.5% in 2011 to 16% in 2015 (> 900% increase). E-cigarettes contain candy flavours (e.g., cherry, chocolate, Turkish delight).

IPHA suggests that the current wording be replaced with the following wording:

The government has an ethical duty to ensure that the media portrayal of the product is appropriately aligned with its known degree of risk. This is dealt with in the recent EU TPD, which aims to harmonise the quality and safety requirements of tobacco products and e-cigarettes for the benefit of consumers. ~~**Although negative health effects from the use of e-cigarettes are currently unknown, there is concern that potential legal liability may be possible if future research finds that negative effects do result from their use. Provided appropriate warnings and information leaflets containing accurate information are included with the sale of any such product, it is difficult to see how a legal action might successfully be taken if this were to occur…**~~ E-cigarettes are not regulated as medicines, have no robust safety and efficacy data, and cannot make any health claims about reducing and preventing use of tobacco. The safety of the inhalation of glycerine and propylene glycol, contained in e-cigarettes, is not well established other than when heated and oxidised propylene glycol can form propylene oxide, which is a known carcinogen. Under the 2014 EU TPD, these products are regulated as "tobacco related products" and forbidden from making any type of health claims. Moreover they are prohibited from sales in pharmacies by our national regulator and not recognized by the World Health Organization as a recognized product to reduce tobacco use. They are noted by the FDA as being rapidly adopted by young people[8].If e-cigarette use becomes socially acceptable, it could lead to increased uptake of nicotine products by people who have never smoked before, later migration to tobacco cigarettes, long-term nicotine dependency, and other potential as yet unknown harms. Therefore, the use and normalisation of these products should not be encouraged.

- The HIQA report states on page 36 that:

  E-cigarettes do not contain tobacco, but provide sensations that are similar to cigarette smoking. This may help smokers achieve long-term abstinence by alleviating some of the sensory and behavioural challenges associated with smoking cessation, as well as helping to reduce nicotine withdrawal symptoms (in cases where the liquid also contains nicotine).

  There is no citation quoted and thus this statement should be removed.

  There is also no discussion or comment regarding use of Glycerin (also called glycerol) for human inhalation. It has been approved for use in food and cosmetics, is also not explicitly approved for human inhalation (German Cancer Research Center, 2013). The discussion is incomplete. A complete discussion can be found on page 16 of the WHO background paper on E-cigarettes (Annex I).

  Regarding inhalation, a Master Data Safety Sheet, guidance for the industrial use of propylene glycol by Sciencelab.com, Inc., states it can cause eye and respiratory irritation and "Prolonged or repeated inhalation may affect behaviour/CNS (with symptoms similar to ingestion) and spleen."(Sciencelab.com Inc., 2013). A major manufacturer of propylene

[8] US FDA: Young people are rapidly adopting e-cigarettes, however, young people who use e-cigarettes are heavier (not lighter) smokers. E-cigarette use among high school students has increased from 1.5% in 2011 to 16% in 2015 (> 900% increase). E-cigarettes contain candy flavours (e.g., cherry, chocolate, Turkish delight).

glycol, the Dow Chemical Company, states in its product safety materials that the "inhalation exposure to [propylene glycol] mists should be avoided" (Dow Chemical Company, 2013) and the American Chemistry Council warns against its use in theatre fogs due to its potential to cause eye and respiratory irritation (The American Chemistry Council, July 2001). When heated and vaporized, propylene glycol can form propylene oxide, an IARC class 2B **carcinogen** (Laino T *et al.,* 2012) and glycerol forms acrolein, which can cause upper respiratory tract irritation (U.S. 12 EPA, Henderson TR *et al.,* 1981). Major injuries and illness have resulted from e-cigarette use, which may be related to lack of basic safeguards in the product design and manufacturing process, as well as the contents of the solution.

- The HIQA report states on page 72 that

  The 2015 Healthy Ireland survey collected data on quit attempts in the last 12 months by current and former smokers. Of current smokers or those that had smoked within the previous 12 months, half (50.0%) had stopped smoking for a day or more in the previous 12 months as part of an attempt to quit smoking. Within the survey, respondents could report the cessation approach they took, choosing from the range of options outlined in Table 3.6…

  However, no reference is provided. Please provide reference cited in Table 3.6.

- The HIQA report states on page 76 that

  From the Healthy Ireland survey data it is apparent that e-cigarettes have become a popular aid for smoking cessation, with almost 29% of quit attempts supported through e-cigarette usage. Unfortunately, these data on e-cigarette use in cessation are limited to a snapshot, and it is therefore not possible to analyse the trends in relation to cessation in Ireland. UK data suggest the use of e-cigarettes for cessation is increasing. Almost all (98%) of e-cigarette users are smokers and former smokers, with the prevalence of e-cigarette usage at approximately 6% in both groups. There is no evidence to suggest that the quantity of cigarettes smoked is less in smokers who also use e-cigarettes compared with smokers who do not use e-cigarettes. Seventy one percent of current smokers who also use e-cigarettes attempted quitting in the previous 12 months, compared with 43% of current smokers who do not use e-cigarettes. Similarly, 66% of current smokers who also use e-cigarettes are either trying to or actively planning to quit, compared with 30% of smokers who do not use e-cigarettes. It is not possible to state whether the higher intention to

  However, no reference is provided. Please provide the reference cited–Healthy Ireland survey data.

- The HIQA report states on page 254 that

  The survey also asked about the dual use of e-cigarettes and tobacco smoking, and found that approximately 15% of smokers also reported using an e-cigarette in the previous 12 months. A systematic review of unassisted quitting in Australia based on 19 Australian

studies reported that 54% to 69% of ex-smokers quit unassisted and 41% to 58% of current smokers had attempted to quit unassisted. This indicates that unassisted quitting is the most popular method of quitting. The authors concluded that public health would benefit from a greater understanding of why so many smokers choose not to use smoking cessation aids.

This survey was taken from http://www.aihw.gov.au/WorkArea/DownloadAsset.aspx?id=60129549848. The statement indicated that 15% of smokers used e-cigarettes in the previous 12 months. Full citation is required to ensure that a full picture is shared. The statement could mislead readers that you could choose e-cigarettes or unassisted quitting and obtain the stated outcome. The Australian Government has previously expressed concerns about the use of e-cigarettes, as the impact of wide scale use of these devices on tobacco use is unknown, and the outcome in the community could be harmful. The Therapeutic Goods Administration (TGA) indicates that use of e-cigarettes may be dangerous and that there has been no assessment of their effectiveness in helping smokers quit. Given their unclear safety profile, e-cigarettes are not currently approved for sale in Australia. This has not been indicated in the citation. A balance view in this case is required.

Refer to Annex 4 for further information

- The Conclusion section of the HIQA report states that

Smoking cessation services should seek to increase the uptake of the use of varenicline (alone or in combination with NRT or bupropion) among smokers wishing to use some type of pharmacological support in their attempt to quit. Although the available results for e-cigarettes are promising, there is insufficient evidence to demonstrate their effectiveness as an aid to smoking cessation at present. It would be appropriate to await the results of ongoing trials before deciding whether e-cigarettes should be recommended for those for whom varenicline is contraindicated, not tolerated or non-preferred. The addition of any type of behavioural support is associated with a beneficial effect on quitting outcomes.

IPHA believes that the HIQA conclusion should reflect the current concerns around unregulated therapies more accurately and rely on evidence based conclusions. NRT is highly regulated as a medicinal product, follows GMP during manufacture and is sold in pharmacies. E-cigarettes are not regulated, are not manufactured under GMP and cannot be sold in pharmacies due to the lack of evidence demonstrating their safety. Therefore, IPHA believes that HIQA should not endorse a product that may carry significant risks to the user and bystanders and that may also have as yet unknown significant side effects. Additionally, the possibility that they may encourage the smoking of cigarettes by children or other adults means that the use and normalisation of these products should not be encouraged.

IPHA suggests that the current wording be replaced with the following wording:

Smoking cessation services should seek to increase the uptake of the use of varenicline ~~(alone or in combination with NRT or bupropion)~~ or NRT among smokers wishing to use some type of pharmacological support in their attempt to quit. The safety and efficacy of NRT for smoking cessation has been long established as confirmed by, amongst others, the Cochrane Collaboration and the National Institute for Health and Care Excellence (NICE) in

England, The WHO has also listed both NRT patch and gum in their Model List of Essential Medicines and their use is endorsed in the WHO Implementation Guideline for Article 14 of the WHO Framework Convention on Tobacco Control. Importantly, in the Irish context, the National Standard for Tobacco Cessation Support Programme published by the HSE also recommends the use of NRT.

The addition of any type of behavioural support is associated with a beneficial effect on quitting outcomes. ~~Although the~~ The available results for e-cigarettes ~~are promising, there~~ is insufficient ~~evidence~~ to demonstrate their any effectiveness as an aid to smoking cessation ~~at present. It would be appropriate to await the results of ongoing trials before deciding whether e-cigarettes should be recommended for those for whom varenicline is contraindicated, not tolerated or non-preferred~~. ~~The addition of any type of behavioural support is associated with a beneficial effect on quitting outcomes.~~ E-cigarettes are not regulated as medicines, have no clinical evidence of safety and efficacy in reducing tobacco use, do not use internationally-recognized good manufacturing and quality standards, are not licenced as smoking cessation aids, are a serious potential health risk, are owned primarily by tobacco companies and are rapidly being adopted by children. Under the 2014 EU TPD, these products are regulated as "tobacco related products" and forbidden from making any type of health claims. Moreover they are prohibited from sales in pharmacies by our national regulator and not recognized by the World Health Organization as a recognized product to reduce tobacco use. They are noted by the FDA as being rapidly adopted by young people[9].If e-cigarette use becomes socially acceptable, it could lead to increased uptake of nicotine products by people who have never smoked before, later migration to tobacco cigarettes, long-term nicotine dependency, and other potential as yet unknown harms. Therefore, the use and normalisation of these products should not be encouraged.

CONCLUSION

As licenced medicines, varenicline, bupropion or NRT products have scientifically proven safety and efficacy profiles, both in relation to individual products and published data supported by a number of years use worldwide, and are manufactured using internationally recognized good manufacturing and quality standards.

E-cigarettes have no such evidence, are owned by tobacco companies, are unregulated, are increasingly being used by children, are actively prohibited from sale in pharmacies by the pharmacy regulator, have no robust evidence of efficacy and have concerns around their safety.

Therefore, we strongly recommend that the HIQA report reflect the aforementioned facts when referring to e-cigarettes. The current inference is that there is an economic benefit to the government in the promotion of the use of e-cigarettes or the promotion of the off-label use of varenicline and NRT in combination. However, there is no such national or international evidence in relation to e-cigarettes by highly esteemed review bodies,

[9] US FDA: Young people are rapidly adopting e-cigarettes, however, young people who use e-cigarettes are heavier (not lighter) smokers. E-cigarette use among high school students has increased from 1.5% in 2011 to 16% in 2015 (> 900% increase). E-cigarettes contain candy flavours (e.g., cherry, chocolate, Turkish delight).

regulators, WHO etc and the use of varenicline and NRT in combination is off label use and the legislation prohibits the promotion of this by pharmaceutical companies. In particular, and in regard to e-cigarette safety, simply not knowing the risk does not mean that there is no risk. In particular, there is no economic benefit to promoting e-cigarette use when their use may increase, not decrease, the number of smokers, lead to significant health and safety issues and lead to a whole new generation of young people becoming addicted to tobacco.

We request that the changes advised in our submission are made to the HIQA report and the associated press release.

APPENDIX 1

EVIDENCE BASED RECOMMENDATIONS

As HIQA deliberates the value and benefits of smoking cessation interventions, we recommend consideration of the value and benefits to public health and the impact on healthcare systems of existing interventions. The following data is demonstrable of the impact of consumer access to NRT medicines.

- Increased access to NRT for all smokers could result in 6 million people giving up smoking in one year, globally, of which 1 million would avoid dying from smoking-attributable causes over their lifetimes.[i]

- In 2009, the WHO placed two forms of NRT on its list of "Essential Medicines," transdermal patches and chewing gum. The WHO examined 13 reviews of the effectiveness of NRTs in reducing and ending tobacco use, and found an increased probability of cessation with NRTs, usually in combination with another cessation strategy.[ii] Specifically, the WHO found that NRTs increase the chances of quitting tobacco use successfully by 58% (Cochrane Review, 2008).[iii]

- Thirty-one countries have national guidelines for smoking cessation treatment, which recommend NRT as an appropriate, evidence-based therapy for smoking cessation.[iv]

- A Cochrane review found that commercially available NRT products are effective methods of smoking cessation, increasing cessation rates by 50-70%.[v]

It is well established that varenicline, NRT or bupropion can reduce the cravings and withdrawal symptoms that occur when stopping smoking, and can increase the likelihood of a successful outcome in those motivated to quit. As licenced medicines, varenicline, bupropion or NRT products have a well-supported safety and efficacy profile supported by a number of years use worldwide. This includes data from a number of placebo-controlled studies reviewed under the medicinal product regulatory framework which have showed them to be effective.

In the absence of a similar level of data and assurance, e-cigarette manufacturers have been unable to address the major issues including:

1. Efficacy Concerns

    - Relative to NRT monotherapy no statistically significant treatment benefit has been demonstrated for e-cigarettes.

2. Safety concerns

- There is an absence of studies on the safety of long-term use of e-cigarettes particularly in terms of contribution towards a substantial reduction in cardiovascular risk factors and respiratory symptoms.
- There are no GMP or minimum standards concerning the quality of for e-cigarette ingredients or control of final product.
- There are no Pharmacovigilance or risk management plan activities in place for e-cigarettes.

3. Promotion concerns:

- Possible promotion of relapse among quitters by suggesting that e-cigarettes are relatively safe.
- Possible increased initiation of smoking, especially amongst young people, by suggesting that e-cigarette smoking (vaping) is safe.
- A large proportion of NRT is used under the supervision of a pharmacist or healthcare professional, with behavioural support being a critical part of the quit attempt. Placing e-cigarettes on the same platform as NRT legitimises its use without any of the same standards or proof of concept.

KEY REGULATOR & OTHER GROUP OPINIONS ON E-CIGARETTES

1. WHO

- The WHO supports the establishment of laws and regulations for Electronic Nicotine Delivery Systems (ENDS), including e-cigarettes. Until they are deemed safe and effective in reducing and stopping smoking and are deemed to be of acceptable quality by national health regulatory bodies, the WHO recommends governments prohibit manufacturers and third parties from making health claims for ENDS, including that ENDS are smoking cessation aids.
- Only products with demonstrated safety and efficacy of reducing and stopping smoking should be registered as medicinal products and be allowed to make smoking cessation claims.

Refer to Annex 1 for further information

4. TGA Australia

- The Australian Government is concerned about the use of e-cigarettes in Australia. The impact of wide scale use of these devices on tobacco use is not known and there is concern that they could be harmful.

Refer to Annex 2 for further information

6. EU Smoking Cessation Guideline

- The lack of reliable studies had led most national authorities to prohibit the promotion of this product as a smoking cessation product.

Refer to Annex 3 for further information

9. British Medical Association (BMA) position

- "While e-cigarettes have the potential to support tobacco harm reduction, any benefits or disadvantages to public health are not yet well established. This reflects the lack of conclusive evidence of their effectiveness as a smoking cessation aid, concerns regarding the variability of the components of e-cigarette vapour, and the absence of a significant health benefit associated with dual use of e-cigarettes and tobacco cigarettes"

Annex 1

WHO ecig_Report_Dec201

Annex 2

ASMI Media Statement on Lancet

Annex 3

ENSP-ESCG_FINAL.pdf

Annex 4

ASMI Media Statement on Lancet

References

[i] WHO. (March 2009). "Proposal for Inclusion of Nicotine Replacement Therapy in the WHO Model List of Essential Medicines." http://www.who.int/selection_medicines/committees/expert/17/application/NRT_inclusion.pdf

[ii] WHO. (March 2009). "Proposal for Inclusion of Nicotine Replacement Therapy in the WHO Model List of Essential Medicines." http://www.who.int/selection_medicines/committees/expert/17/application/NRT_inclusion.pdf

[iii] WHO. *Tobacco Free Initiative (TFI).* http://www.who.int/tobacco/quitting/summary_data/en/

[iv] Raw M and Slevin C. (Dec 7, 2007). "A survey of tobacco dependence treatment guidelines and systems in 45 countries." http://www.treatobacco.net/en/uploads/documents/Publications/Raw%20&%20Slevin%202007%20survey%20on%20treatment%20guidelines%20and%20services%20in%2045%20countries.pdf

[v] Stead LF, Perera R, Bullen C et al. *Cochrane Database Syst Rev.* (2012). "Nicotine replacement therapy for smoking cessation." http://www.cochrane.org/reviews/en/ab000146.html