

RESPONSE TO CONSULTATION LETTER MLX 364

THE REGULATION OF NICOTINE CONTAINING PRODUCTS

**Made on behalf of
DIGITAL DYNAMICS INTERACTIVE SOUND & VISION LIMITED**

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1	EU: Case C-319/05 <i>Commission v Germany</i>
2	<i>Smoking Everywhere Inc and Sottera Inc, d/b/a NJoy v. U.S. Food and Drug Administration</i> [Civil Case No. 09-771 (RJL)]
3	Poisons Rules 1982 (SI 1982/218)
4	Email on behalf of e-cigs.co.uk titled 'Global Public Health Alert', regarding misinformation originating from LACORS' press release dated 13 May 2010
5	ANALYZE Report, <i>NJoy Study to Determine Presence of TSNAs in NJOY Vapor</i> , dated 9 December 2009
6	Exponent, Technical Memorandum Technical Review and Analysis of FDA Report: "Evaluation of e-cigarettes", dated 30 July 2009
7	Scientific Analysis Laboratories Certificate of Analysis for Digital's e-cigarette nicotine containing fluid, dated 6 May 2009 and LPD Lab Services Test Report Analysis of Components from "e-Juice XX HIGH 36mg/ml rated Nicotine Solution" ref S 55434, dated 11 June 2009
8	Stepanov, I. Jensen, J. Hatsukami, D. and Hecht, S.S. (2005) "Tobacco-specific nitrosamines in new tobacco products", <i>Nicotine & Tobacco Research</i> , Volume 8, Number 2 (April 2006), pp. 309 - 313.
9	Email from Clare Hedges of the MHRA dated 16 April 2010

1 Executive Summary

Introduction

- 1.1 Digital Dynamics Interactive Sound & Vision Limited, trading as e-cigs.co.uk and liberro.co.uk, (“Digital” or “we”), a distributor of electronic cigarettes (“e-cigarettes”), are writing in response to Consultation Letter MLX 364 on whether to bring all nicotine containing products (“NCPs”) within the medicine licensing regime, which would require all currently unlicensed NCPs on the market to apply to the Medicines and Health Regulatory Agency (“MHRA”) for a medicines marketing authorisation (“MA”). For the reasons outlined below, we favour the MHRA’s Option 3 to allow products containing nicotine not licensed under the medicines regime to remain on the market under the existing regulatory structure.¹
- 1.2 NCPs provide a real alternative to smoking cigarettes and are similarly a consumer product. They are not a medicinal product within the definition in Article 1(2) of Directive 2001/83/EC. The current regulation under product safety legislation and the Poisons Act 1972 (“Poisons Act”), combined with Trading Standards Institute’s extensive powers provide a sufficient safeguard to public health.
- 1.3 The MHRA’s preferred option is:
- “Option 1 - Whether products containing nicotine should be considered by the Agency to be medicinal products by function and, if so, whether all unlicensed NCPs should be removed from the market within 21 days. [...]”*
- 1.4 The MHRA has failed to substantiate that further regulation of NCPs is proportionate to the need to safeguard public health and Option 1 and Option 2 may be illegal under Community Law.
- 1.5 Summarised below are the key arguments that we rely on in asserting that removing these products from the market is not in the interests of public health:
- (a) Definition of medicinal products by function: NCP products are not designed or used as medicinal products and harm reduction is not a valid reason to classify a product as a medicine. Further details are provided in Section 2 below.
 - (b) Harm reduction and Nicotine Replacement Therapy (“NRT”): the sources cited by the MHRA indicate that a move toward a harm reduction approach requires alternatives to cigarettes to be made more readily available. Regulating NCPs more heavily will create the absurd situation whereby cigarettes, the most dangerous nicotine delivery method, will be the least heavily regulated. Further details are provided in Section 3 below.
 - (c) The existing regulatory framework: nicotine is regulated at levels harmful to humans under the Poisons Act and delivery methods such as those used in NCPs are explicitly referred to. General product safety legislation, as enforced by Trading Standards, includes adequate powers to remove unsafe products from the market. Further details are provided in Section 4 below.
 - (d) Safety: the evidence relied on by the MHRA does not reflect the limited danger NCPs pose, the evidence is in some cases fundamentally flawed and in other cases heavily biased (e.g. failing to note that the trace levels of carcinogens apply equally to licensed NRT products). Further details are provided in Section 5 below.

¹ Please note that Digital feels that the consultation process has not been carried out in a fair and proportionate manner and not in accordance with the Hampton Principles. In particular the drafting of Option 3 is clearly leading those who engage in the consultation toward deciding in favour of the MHRA’s preferred Option 1.

- (e) Efficacy and quality: the key argument cited by the MHRA that a failed quit attempt will negatively affect a future quit attempt appears to have no scientific grounding. Neither is the argument for lack of efficacy and quality supported by relevant up-to-date evidence. Further details are provided in Section 6 below.
- (f) Impact assessment: the risk assessment in MLX 364 is very limited and does not comply with the standards expected of public consultations. The true cost of obtaining an MA is not reflected in the consultation document and calculations for the health benefit of the proposal are arbitrary. The consultation does not substantiate a clear case for the need to protect public health and is not proportionate to the danger posed by NCPs. Further details are provided in Section 7 below.

Definition of a medicinal product

- 1.6 The MHRA bases its decision to bring unlicensed NCPs within the medicine licensing regime on the grounds that NCPs are a medicinal product. The EU definition of a medicinal product has two limbs:

“[a] Any substance or combination of substances presented as having properties for treating or preventing disease in human beings.

[b] Any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis.”²

- 1.7 The MHRA currently assess medicines under limb a), by presentation. Currently producers of NCPs do not advertise their products as medicinal products, specifically stating they are not designed for smoking cessation, and have been selling their products safely for a number of years. However MLX 364 proposes that NCPs should be regulated by their function, which the MHRA concedes “*represents a major departure from relying on the regulation of these products by claim*”³. The need for a major shift in policy has not been substantiated and Digital disagrees with the proposed change on both legal and policy grounds.
- 1.8 The definition of medicinal products, under limb b), in Article 1(2) of Directive 2001/83/EC states that a product must have as its purpose restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action or making a medical diagnosis. The directive was implemented in England and Wales by the Medicines for Human Use (Marketing Authorisations Etc) Regulations 1994.⁴ Unlicensed NCPs are clearly not intended for these purposes, rather they are consumer products used predominantly as:
1. a permanent substitute for conventional tobacco smoking; and
 2. a temporary substitute for conventional tobacco smoking in areas and situations where it is not permitted or convenient to smoke.
- 1.9 The European Court of Justice (“ECJ”) has ruled “[...] *it is not sufficient that product has properties beneficial to health in general, but it must strictly speaking have the function of treating or preventing disease.*”⁵ E-cigarettes certainly do not have the effect of “treating” or “curing” nicotine addiction as the e-cigarette is a very effective method (both in its technical operation and its product presentation) of very closely mimicking the self-dosing nicotine “hits” of tobacco smoking.

² Article 1(2) of Directive 2001/83/EC

³ Para. 14 MLX 364

⁴ SI 1994/3144

⁵ EU: Case C-319/05

That unlicensed NCPs are not medicinal products is reinforced by the secondary enjoyment consumers obtain from these products, in common with consumer products but not usually medicinal products. A clear distinction can be drawn on these grounds between e-cigarettes and Johnson & Johnson's Nicorette Inhalator product, which is clearly intended as a medicinal product and has few of the recreational aspects presented by e-cigarettes. The failure of the MHRA to set out the legal grounds on which it claims that NCPs are medicinal by function represents a clear failure in the consultation⁶, particularly in light of the ECJ's clear views on this matter⁷.

- 1.10 In the United States, where there is a similar definition of medicinal product by function, in a recent decision Judge Richard J Leon held that e-cigarettes were clearly not medicinal products⁸. Judge Leon not only held that NCPs that did not claim to have health benefits were not medicinal products, but also commented on their functional similarity to cigarettes, stating that they should therefore be regulated on this basis. The court did not find the U.S. Food and Drugs Administration's ("FDA's") evidence that the products posed a public health risk convincing. The MHRA rely heavily on this same evidence in MLX 364.

Nicotine replacement therapy and harm reduction

- 1.11 The decision to regulate NCPs on the grounds that they can be used to effect harm reduction, would create the absurd result that products not claiming to be medicines would be more heavily regulated than cigarettes, which are far more dangerous than NCP products. The MHRA has not justified, firstly that harm reduction is a legal reason for a product to be a medicine, and secondly why cigarettes fall outside of the medicinal regime, if products are included on the common factor of containing nicotine.
- 1.12 The MHRA's decision to heavily regulate unlicensed NCPs on the basis of the Department of Health's ("DoH's") strategy of harm reduction seems somewhat counterintuitive for two reasons. Firstly it is widely recognised, as stated in MLX 364, "[...] *in terms of harm reduction, effective alternatives need to be considered that allow an individual to obtain nicotine without being subjected to the risks of smoked tobacco, and that pure nicotine products currently available as NRT are considerably safer than smoked or smokeless tobacco products.*"⁹ E-cigarettes and other unlicensed NCPs are far more attractive in this regard than nicotine replacement therapy ("NRT") products¹⁰. If producers are required to get a MA, the cost of gaining authorisation will effectively result in removal of these products from the market. This may force current consumers of unlicensed NCPs back to conventional cigarettes, which are known to be harmful. Secondly, the long-term success rate of NRT has been questioned in a number of peer review studies, where the long term success rate has been estimated at as low as 7%¹¹. In addition there is substantial evidence that a significant minority of GPs in the UK do not recommend patients to NHS Stop Smoking Services nor believe in the efficacy of NRT products¹².

⁶ Para. 14 n 3 above

⁷ The MHRA has not provided a proportionate response nor provided sufficient evidence that the regulation of these products are necessary for the protection of public health.

⁸ Civil Case No. 09-771 (R.JL). Please note that, while Judge Leon's decision stands, a stay has been granted on his judgment until the FDA's appeal against the decision is heard. Notably despite the FDA's ability to continue to detain these products and refuse entry, an e-cigarette shipment from the UK was detained at the U.S. border by the FDA, who sent samples away for testing. Once the test results came back, the shipment was allowed through.

⁹ Para. 11 n 3 above citing the BMA Board of Science's policy position

¹⁰ See n 8 above

¹¹ See Section 3, n 42 below

¹² Vogt, F. Hall, S. and Marteau, T. (2006) "General practitioners' beliefs about effectiveness and intentions to prescribe smoking cessation medications: qualitative and quantitative studies", *BMC Public Health*, 2006, 6:277, doi: 10.1186/1471-2458-6-277, 8 November 2006. Available at: <http://www.biomedcentral.com/1471-2458/6/277>

- 1.13 The Royal College of Physicians (“RCP”) notes that smoked tobacco, the most hazardous product containing nicotine, is freely available. Furthermore a number of smokeless tobacco products that are not intended to be sucked, some of which have significant hazard profiles, can be purchased as freely as smoked tobacco products and are unregulated. The RCP draws the conclusion “*that the current regulatory system perpetuates smoked tobacco as the most freely available, affordable, effective and widely used nicotine delivery product. [...] the current regulatory system therefore favours the most dangerous tobacco products over those that are less hazardous, while imposing the strictest restrictions on medicinal nicotine*”¹³. The MHRA’s plans to regulate products on the basis of harm reduction clearly runs against the RCP’s sentiments; not only making it more difficult for persons to effect a harm reduction strategy, but also add to “*the grossly inconsistent regulation*”¹⁴ of nicotine products.
- 1.14 At paragraph 21 MLX 364 the MHRA states that where a person uses NCPs, which have not been properly tested, and fails to quit that this is likely to damage future quit attempts. However the Expert Working Group on Harm Reduction and NRT of the Commission on Human Medicines (“WG”), on the contrary, found that there was a lack of data on this point but that available evidence pointed toward a reduction in smoking being beneficial to future quit attempts¹⁵. On this basis the argument for unlicensed NCP’s needing regulation on grounds of their quality and efficacy seem unfounded, because even temporary smoking cessation may benefit rather than deter future quit attempts.
- 1.15 Furthermore without the additional measure of a Banning Order¹⁶, there is a risk that regulating NCPs would simply encourage the purchase of NCPs on the internet or via a black market, particularly considering that NCPs are unregulated in a number of key EU jurisdictions including Germany and The Netherlands. The MHRA notes this risk in the key assumptions/sensitivities/risks section of MLX 364 and also indicates that it would have little power to prevent the sale of NCPs in the above manner.
- 1.16 Nicotine has not been found to be a dangerous drug, in fact MLX 364 states “*a body of evidence is emerging that suggests that nicotine, while addictive, is actually a very safe drug*”¹⁷. The trend in the regulation of NRT is further evidence of the changing perception of nicotine. Initially NRT was a prescription only drug, this moved toward sale on an over the counter (“OTC”) or general sale (“GSL”) basis. Now all NRTs are available GSL, even to pre-teen children and pregnant women. The MA of the Nicorette Inhalator was granted on a harm reduction basis and the MHRA has invited further applicants to apply on this basis. This may well represent a ‘step-wise’ approach to nicotine regulation. However it cannot help but be interpreted as an indication of the relative danger that nicotine represents to public health. A move toward regulating unlicensed NCPs as medicines on the grounds that they are harm reduction devices, a move that is in stark contrast to the decreasing trend in the level of regulation of NRT, is clearly disproportionate to the harm posed by nicotine.
- 1.17 The MHRA has grouped all NCPs together on the ground that they contain nicotine; which seems to be an incomplete definition when tobacco products are excluded. In defining NCPs as medicines because they contain nicotine, the MHRA has failed to adequately explain why tobacco

¹³ Royal College of Physicians, London, Tobacco Advisory Group (2008) “Ending tobacco smoking in Britain: Radical strategies for prevention and harm reduction in nicotine addiction”, September 2008. Available at: <http://bookshop.rcplondon.ac.uk/contents/a7b2d652-288a-4c13-bc7b-25bf06597623.pdf>

¹⁴ Ibid

¹⁵ P. 3 5.5 Commission on Human Medicines Working Group on Harm Reduction & Nicotine Replacement Therapy minutes of 14 October 2009 meeting

¹⁶ P.18 n 3 above

¹⁷ Para. 11 n 3 above

fall outside this definition even though they also contain nicotine, especially considering that the nicotine in NCPs is extracted from tobacco. There are significant differences between different nicotine delivery devices, for example e-cigarettes differ significantly from the Nicorette Inhalator both in the means by which the nicotine is administered and the products' intended use. E-cigarettes use a propylene glycol base, administered with heat. On the other hand the Nicorette Inhalator is water based and does not use heat. E-cigarettes are intended as an alternative to smoking tobacco, whereas the Nicorette Inhalator is a product designed to aid NRT, this explains why the latter offers little in the way of consumer enjoyment. E-cigarettes bear greater similarity to smoked tobacco products than NRT products, except that e-cigarettes can effect harm reduction by offering a non-combustible substitute or partial substitute to smoking.

The existing regulatory framework

- 1.18 The current regulatory structure provides authorities with adequate powers to bring manufacturers that are selling dangerous or substandard products to task. The Poisons Act provides for the immediate withdrawal of products from the market and criminal prosecution of those responsible where a product is found to contain toxic levels of nicotine¹⁸. The level at which nicotine content is classed as toxic is 7.5%, the strongest nicotine liquid cartridge available in the UK is 54mg/ml (and even this product recommends dilution), which is considerably below the 75mg/ml at which nicotine levels are considered to be toxic. If NCPs truly contained dangerous levels of nicotine they could already have been removed from the market; the fact that this has not happened indicates that unlicensed NCPs pose little real threat (reinforced by the complete absence of instances of harm to users of these products). These rules are supplemented by the general product safety legislation and regulation by the Trading Standards Institute ("Trading Standards"), who have been ensuring CHIP compliance, electrical safety and Good Manufacturing Practice of unlicensed NCPs.
- 1.19 LACORS' concerns over e-cigarettes seem to be grounded primarily in the inapplicability of tobacco legislation to e-cigarettes. LACORS' preferred mode of regulating e-cigarettes is the amendment of tobacco legislation to include e-cigarettes within the definition of tobacco products. This, it is claimed, would assist regulatory officers in the key problems they have encountered: CHIP compliant packaging, adequate hazard labelling and the promotion/advertisement of the product. However despite the similarity in the use of cigarettes and e-cigarettes by consumers, regulation in this manner is not appropriate: e-cigarettes are not tobacco products. Another concern raised by LACORS is that variations on the product keep appearing, each requiring individual testing to assess compliance with product safety legislation, but in this regard e-cigarettes are no different to other products subject to technical variation. Prudent self-regulation by producers of e-cigarettes has resulted in the following measures being commonplace:
- e-cigarettes are usually sold in CHIP-compliant packaging, despite containing well below 'toxic' levels of nicotine;
 - child-proof caps on supplies of nicotine-containing cartridges and/or 'e-liquid' bottles of nicotine liquid;
 - explicit warnings are displayed on the majority of legitimate retailers' websites, advising potential customers that e-cigarettes are not smoking cessation devices, but rather offer an alternative to traditional tobacco smoking;
 - measures have been put in place not to sell to persons under the age of 18; and
 - CoSHH hazard warning signs and tactile safety warning triangles are also included on the labelling to alert consumers (including the blind and partially-sighted) to the potential risks associated with handling nicotine.

¹⁸ Poisons Act 1972 and associated legislation, see Section 4.

1.20 These measures are notably absent from existing licensed NRT products, which are usually not sold in child-proof packaging, and are increasingly handed out to children in schools. Furthermore, the NCP producers welcome sensible and proportionate regulation of their products and are happy to work with Trading Standards toward Codes of Practice and the like, but the current proposal goes too far as it would effectively remove them from the market. In fact Trading Standards officers have been appreciative of the measures taken by Digital and other distributors and, of those officers consulted, are not at all concerned with the efficacy of the current regulation of NCPs.

Safety

1.21 In questioning the safety of NCPs the MHRA has relied heavily on the findings of the United States Food and Drugs Administration (“FDA”). The FDA in its 4 May 2009 report found detectable levels of tobacco specific nitrosamines (“TSNAs”). However the FDA’s report fails to mention that these are not present at harmful levels. As the nicotine is derived from tobacco some of the carcinogenic products found in tobacco are invariably retained along with the isolated nicotine, but are present at levels low enough that they have been found not to present a health risk¹⁹. Current NRT products contain TSNA’s at roughly the same levels as unlicensed NCPs, providing further evidence that they are considered by the medical community not to be harmful, or at least less harmful than smoking cigarettes. The World Health Organisation’s (“WHO’s”) recommendations referred to by the MHRA in MLX 364 have been superseded by current thinking on a harm reduction approach to nicotine addiction and studies into the safety of NCP products. Digital’s e-cigarettes contain levels of the substances flagged as problematic by the MHRA at levels similar to, or lower than those found in ‘NJoy’, a U.S. brand of e-cigarette: substantial evidence was presented in Civil Case No. 07-771 (RJL) as to NJoy’s safety. The FDA’s evidence has been criticised by public health experts.

1.22 The FDA also claimed to identify di-ethylene glycol, in one sample (not that of NJoy). However, the FDA fails to note that di-ethylene glycol is an accepted ingredient in tobacco cigarettes and at considerably higher concentrations than that found in one out of sixteen cartridges tested by the FDA. Other than the single example cited by the FDA, e-cigarettes contain propylene glycol not di-ethylene glycol. There seems to be some confusion between these two chemicals, perhaps due to the common ending ‘glycol’. E-cigarettes contain propylene glycol, which is used to dilute the nicotine in the solution that can then be delivered to the smoker as a vapour. Propylene glycol is a safe and inert substance commonly used as a food additive and is an ingredient in many common products (please see paragraphs 5.11 - 5.15). For example, propylene glycol is the substance that produces the fog generated by fog machines. The toxic substance di-ethylene glycol found in antifreeze is a completely different substance.

1.23 The LACORS in its 13 March 2009 press release²⁰, claimed to have found dangerously high levels of nicotine in the NCPs it examined. However the report contained a fundamental error, a misunderstanding of the SI system that resulted in overestimation of the concentration of nicotine in the products tested. A typical refill will hold 18mg/ml of nicotine, LACORS thought this to be a concentration of 20%. It is in fact 1.8% (a concentration significantly below the 7.5% toxic level): 200mg/ml is required for a 20% concentration. Digital have issued a letter to LACORS requesting that they retract their press release, but LACORS have not responded²¹.

¹⁹ See Section 5 para. 5.2

²⁰ LACORS press release dated 13 March 2009. Available at: <http://www.lacors.gov.uk/lacors/PressReleaseDetails.aspx?id=21233>

²¹ Please see para. 4.7 below

- 1.24 As such the MHRA have not substantiated on the evidence provided that greater regulation of unlicensed NCPs is required to safeguard public health, which is the legal standard required as set out in Case C-319/05.

Efficacy and quality

- 1.25 There appears to be no evidence to substantiate the MHRA's claim that failed quit attempts negatively affect future quit attempts. The design of e-cigarettes allow users to self dose, the very nature of nicotine addiction will result in a person using the product until the desired result is achieved and if the product is not working the user will notice this.
- 1.26 Finally Digital serves a customer base of approximately 30,000 UK residents including many repeat customers. The number of users of e-cigarettes in the USA has been estimated at as high as 1 in 40 smokers²². Not only does this, combined with the lack of incidences of harm, suggest that e-cigarettes are safe products, but also that they are found by consumers to be effective.

Impact assessment

- 1.27 The MHRA's impact assessment does not adequately assess the true cost and time associated with a manufacturer obtaining a MA. MLX 364 does not mention the cost and time associated with sufficient clinical trials to achieve medical status, merely mentioning the fees payable to the MHRA, a tiny proportion of the total cost. The implementation of the MHRA's option 1, removal of unlicensed NCPs from the market within 21 days, is clearly a disproportionate response to a product that has not been shown to be a threat to public health. It would effectively remove all current producers of unlicensed NCPs from the market, to the advantage of large pharmaceutical companies. On the contrary the MHRA argues that the products when licensed can be used as a part of a harm reduction strategy. Option 2, removal of unlicensed products after a certain period (of one year), would have a similar effect due to the length of time required to get a MA.
- 1.28 The MHRA has not complied with the Hampton Principles²³ by carrying out a comprehensive risk assessment and therefore a clear case for protection has not been substantiated. Furthermore the consultation was inevitably carried out during an election period against the Office Election Guidance. A number of the sources that the MHRA have relied on in MLX 364 have been found lacking in their scientific analysis, in particular the report by the FDA and the LACORS press release. The impact assessment does not adequately assess the cost to producers of NCPs and then goes on to attempt to quantify the saving to public health, which is based on unquantifiable assumptions. The calculation is based on the premise "*that the proposed regulation would bring about additional smokers who successfully quit using licensed NRT products*"²⁴. The MHRA then goes on to explain that their calculation assumes that 1,312 persons will quit using licensed NRT products. This assessment is arbitrary and wholly inadequate. It does not factor in those who cease smoking using unlicensed products. Neither does it explain why existing NRT products cannot adequately service the needs of those who choose to quit. It may be that the MHRA intends to argue that people may fail to quit because of the efficacy of unlicensed NCPs, but as discussed above the WG does not believe that failed quit attempts affect future quit attempts (on the evidence available), nor would the evidence be sufficient to quantify its cost saving in this manner.
- 1.29 Finally the ECJ have held, in Case C-319/05, that "[t]he issuing of a marketing authorisation under Article 8 of Directive 2001/83 is subject to particularly strict requirements, and the obligation to

²² 24-7 press release: "Electronic Cigarettes Now Used By 1 in 40 Smokers", Tiffany Ellis, 4 March 2010 <http://www.24-7pressrelease.com/press-release/electronic-cigarettes-now-used-by-1-in-40-smokers-139952.php>

²³ Para. 5.8 n 15 above

²⁴ Para. 21, 3 'Evidence Base (for summary sheets)'

obtain such an authorisation before being able to market the product concerned in the territory of the Member State cannot be regarded as being in accordance with the principle of proportionality unless it is actually necessary to safeguard public health.”²⁵ The MHRA have not satisfied this standard and the introduction of this measure could be found to be a measure having equivalent effect to a quantitative restriction within the meaning of Article 34 of the Treaty for the Functioning of the European Union (“TFEU”).

²⁵

Page 3 n 5 above

2 The proposed change of regulation

2.1 The MHRA wishes to withdraw all unlicensed NCPs from the UK market with effect from June 2010 (preferred Option 1 in MLX 364), this proposal pivots around one key element: the re-classification of NCPs as a medicine.

Definition of a medicinal product

2.2 Article 1(2) of Directive 2001/83/EC gives the following definition of a medicinal product:

“[a] Any substance or combination of substances presented as having properties for treating or preventing disease in human beings.

[b] Any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis.”

2.3 The directive was implemented in England and Wales by the Medicines for Human Use (Marketing Authorisations Etc) Regulations 1994²⁶, Regulation 3(1) states:

“Except in accordance with any exception or exemption set out in the relevant Community provisions and subject to [paragraphs 1 and 3 to 5A] of Schedule 1—

(a) no relevant medicinal product shall be placed on the market; and

(b) no such product shall be distributed by way of wholesale dealing,

*unless a marketing authorization in respect of that product has been **granted in accordance with the relevant Community provisions** by the licensing authority or the European Commission, and is for the time being in force in accordance with those provisions.”* (emphasis added)

MHRA change of policy

2.4 The MHRA have up until now relied on a) – the so called “Presentation Limb”, to the exclusion of b) - the so-called “Functional Limb”. As most UK e-cigarette retailers currently do not make therapeutic claims for their products e-cigarettes are outside of the MHRA’s regulatory authority. This has not changed and has been going on safely since the introduction of these products a number of years ago.

2.5 For reasons that are not adequately explained or justified in the MLX364 document, the MHRA has suggested that they would now like to rely on b), the functional limb and therefore admit e-cigarettes as a medicine requiring MA licensing.

Tobacco regulation

2.6 Tobacco is regulated outside of the controlled drugs and medicinal regimes. There is tobacco, specific regulation controlling product regulation, labelling, and advertising and promotion. These deal predominantly with the dangers of smoking. Tobacco products are also regulated under general product legislation. Nicotine is not controlled under the tobacco regime; neither is it a controlled drug under the Misuse of Drugs Act 1971 and associated legislation (as nicotine is not considered a dangerous recreational drug). However nicotine is effectively regulated under the Poisons Act which accounts for human consumption: if nicotine is sold at poisonous levels a criminal offence is committed (see below for further details). The MHRA, because they cannot

²⁶ See n 4 above

regulate NCPs under tobacco legislation claim that they are medicinal products, whereas they are in fact alternative nicotine delivery systems to smoking cigarettes.

- 2.7 It is unsustainable to argue that a product is a medicine by virtue of its containing nicotine, since tobacco also contains nicotine and is clearly not a medicine. Similarly, to argue that any product containing nicotine that is not a tobacco product effects harm reduction ignores the essential aspect of the definition of a medicinal product: it must be used to make a medical diagnosis or to restore, correct or modify physiological functions.

Scope of Article 1(2) of Directive 2001/83/EC

- 2.8 Article 1(2) of the Directive's definition of a medicine is deliberately broad to capture "borderline" products. However, since most normal food and drink items in the human diet will exert a metabolic action (and possibly a pharmacological and/or immunological action) it was clearly not the legislators' intention to classify such a broad range of products as medicinal products.

Distinction between a medicine and non-medicine product or substance

- 2.9 It is clear from a common sense reading of the second limb of Article 1(2) of the Directive that it is drafted broadly regarding its effects on human beings. However it is drafted more narrowly in relation to the purpose such effects must have:

*"Any substance or combination of substances which may be used in or administered to human beings either **with a view to** restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis."* (emphasis added)

- 2.10 In this instance the phrase "with a view to" is a legal term whose plain English meaning is "with the aim or intention of" or "with expectation or hope of". Therefore for a product to be a medicine it must be sold and/or used with the intent of being therapeutic in one of the ways mentioned in limb b) of the definition.

- 2.11 This is confirmed and expanded upon in the ruling of the ECJ of 15 November 2007 (C-319/05), attached at **Annex 1** in particular paragraphs 61 and 64 shown below.

*"61. Contrary to the definition of medicinal product by presentation, whose broad interpretation is intended to protect consumers from products which do not have the effectiveness they are entitled to expect, the definition of medicinal product by function is designed to cover products whose pharmacological properties have been scientifically observed and which are **genuinely designed** to make a medical diagnosis or to restore, correct or modify physiological functions [...].*

64. In those circumstances, and in order to preserve the effectiveness of that criterion, it is not sufficient that a product has properties beneficial to health in general, but it must strictly speaking have the function of treating or preventing disease. (emphasis added).

- 2.12 The ECJ goes even further by stating that consideration of the potential risks related to the use of the product must be taken in light of Community Law, in particular Directive 2001/83²⁷.

- 2.13 The MHRA claim to have the authority to regulate NCPs on the following grounds:

"Legal advice is that prima facie nicotine falls within medicines legislation in terms of its pharmacological action (medicinal by function). Whether or not a nicotine containing product falls to be considered as a medicinal product by function depends on factors going beyond the product having an appreciable effect on metabolism. These include

²⁷ Para 70 n 5 above

the manner in which the product is used, the extent of the products distribution, its familiarity with consumers and the risks which its use may entail.”

- 2.14 However this statement doesn't adequately reflect the legal position established by the ECJ in the case HLH Warenvertriebs GmbH v Germany (C-211/03). In this case the ECJ stated that whether a product is a medicine is to be decided on a case-by-case basis and sets out factors that require consideration in coming to this conclusion:

“Products to which the definition is applied by virtue of their 'function' must first be subjected to a detailed technical and scientific investigation. In its case-law the Court has mentioned the following criteria which may be taken into consideration in determining whether a product is covered by this part of the definition: the pharmacological properties of the product concerned in the present state of scientific knowledge, the manner in which it is used, the extent of its distribution, its familiarity to consumers and the risks which its use may entail.”²⁸

The court also stated:

*“The pharmacological effect of a product is one of the factors that must be investigated in assessing whether a product has a significant influence on the metabolism and can affect the actual functioning of the organism and thus, in the language of the second subparagraph of Article 1(2) of Directive 2001/83, may be administered to human beings with a view to making a medical diagnosis or to restoring, correcting or modifying physiological functions in human beings. The risks associated with the use of the product constitute one of the factors which may be taken into account in determining whether or not it is a medicinal product. (26) However, this factor is not decisive. At least one demonstrable 'therapeutic effect' must also be present. **The therapeutic efficacy must always be investigated in relation to the risk associated with the use of the product.**”²⁹ (emphasis added)*

- 2.15 The MHRA's statement is clearly contrary to the ruling of the ECJ above. As the MHRA has not disclosed the substance or reasoning of the legal advice it has received, it should be disregarded for the purposes of the consultation.
- 2.16 Clearly in assessing whether a product is a medicinal product by function these factors must be taken into consideration with the aim to identify products genuinely designed to make a medical diagnosis or to restore, correct or modify physiological functions. The potential danger posed by the product is not a relevant factor outside of these considerations. The analysis below shows clearly that e-cigarettes do not satisfy this requirement.
- 2.17 We further refer to the European Commission's Orientation Note³⁰ that cites case C-319/05 in the specific context of the e-cigarette on page 4: “[...] where the Court goes a step further and sets out that the definition of medicinal product by function covers products **which are genuinely designed to make a medical diagnosis or to restore, correct or modify physiological functions; the product under assessment must have the function of treating or preventing disease [...]**” (emphasis added).

Restoring, correcting or modifying physiological functions

²⁸ Para 51 HLH Warenvertriebs GmbH v Germany (C-211/03)

²⁹ Ibid para 30

³⁰ The Health & Consumer Protection Directorate-General EU Orientation Note Electronic cigarettes and the EC Legislation (dated 22May 2008)

2.18 It is not in contention that nicotine is a modifier of physiological functions, by exerting significant pharmacological, immunological and metabolic actions. These effects have been studied *in vivo* in both tobacco smokers and users of NRTs with nicotine supplied at lower doses than average cigarette smokers. However the effects are identical (or less than) those experienced by those smoking cigarettes and it is not proposed that normal cigarettes need to be brought within the MA regime. There is therefore no justifiable basis to bring NCPs within the MA regime for this reason either.

2.19 The design of the e-cigarette is to deliver nicotine at similar doses and frequencies to smokers who “puff” on a cigarette. Additionally users self-dose until they feel satisfied, it is therefore *prima facie* likely that all of the above actions will be mostly similar to those experienced by tobacco smokers.

For what purpose is an e-cigarette manufactured, sold and used in “normal” usage? Is it sold or used as a “medicine”?

2.20 The information currently available indicates that for both the manufacture and distribution of the product and the end user consumption that e-cigarettes are not intended as a medicinal product.

Manufacture and distribution

2.21 Manufacturers of e-cigarettes are not pharmaceutical companies nor do they purport to be manufacturers of medical devices or any other medicinal products. In fact on distributors’ websites there is typically a warning about the use of the product, for example Digital’s website states:

*“There are many myths surrounding the electronic cigarette, some perpetrated by less scrupulous suppliers determined to make a sale at any cost. An e-cigarette cartridge is not equivalent to a whole packet of cigarettes, e-cigs don’t just produce water vapour and **they are not designed to be a smoking cessation device.** If your e-cig supplier states these as fact, it would be wise to find a more clued-in (or honest) supplier!”³¹ (emphasis added)*

2.22 Distributors and Retailers do not claim to be offering medical products, nor do they make claims that their products can treat, cure or otherwise mitigate any disease.

2.23 It is not apparent that manufacturers, distributors or retailers carry out medical research nor do they employ such research personnel. There is evidence that some of these companies have commissioned and paid for scientific or medical tests and trials to establish such matters as product quality, safety etc. However, none of this work has been commissioned for the purpose of creating a cure for any known disease.

End user consumption

2.24 The e-cigarette is used by the vast majority of its users as a substitute for tobacco smoking either:

1. as a permanent substitute for conventional tobacco smoking; or
2. as a temporary substitute for conventional tobacco smoking in areas and situations where it is not permitted or convenient to use tobacco – i.e. areas covered by the smoking ban or friends homes etc.

2.25 Other indicators that e-cigarettes are not medicinal products include that consumers derive a perceived consumer benefit from the product such as generated by the product’s operating functions (vapour generation etc), the large range of products, colour and design, accessories and differing strengths and flavours of ‘e-liquid’ (the chemical component of the system that contains

³¹ Source <http://www.e-cigs.co.uk/electronic-cigarette-myths.html>

nicotine). This appears to add to the ‘hobby’ type enjoyment often displayed by enthusiasts, be it ‘coffee aficionados’ or ‘vintage car buffs’. This secondary enjoyment is often displayed in general consumer products, but is not normally found in medical products. Existing licensed NRTs appear to present a user experience that is at best neutral and often slightly unpleasant, for example, many think NRT gum is distasteful with a product presentation and packaging that make the product look and feel like a medical product.

- 2.26 This enhanced “user experience” adds to and reinforces the recreational enjoyment of the e-cigarette in addition to its primary purpose of efficient nicotine delivery. This ‘consumer product type’ enjoyment encourages and motivates users to switch from smoked tobacco products and to continue using the product, and therefore achieves the DoH’s and MHRA’s goal of harm reduction, in a way that existing licensed NRT products do not. However, it is evident that this does not go toward treating the disease of nicotine addiction.
- 2.27 On the basis of the product description and end user consumption NCPs are used legally as a delivery system for a recreational psychoactive drug, nicotine, with a secondary benefit of being an enjoyable hobby for many users and a generally enjoyable product to use.
- 2.28 The MHRA goes so far as to state nicotine is “*actually a very safe drug*”³². It would appear that the majority of users, whilst acknowledging the powerful addictive properties of nicotine, wish to continue to use this safe drug without the currently well established and understood risk to health caused by tobacco smoking.
- 2.29 Current consumer usage of e-cigarettes therefore seems to indicate that consumers are not using the product to cure or treat a disease. Even if some users did believe that the product was helping them treat or cure something it is difficult to identify any such disease. It is certainly not “treating” or “curing” nicotine addiction as the Electronic Cigarette is a very effective method (both in its technical operation and its product presentation) of very closely mimicking the self-dosing nicotine “hits” of tobacco smoking. It is therefore a very efficient method of maintaining nicotine addiction. This is the key distinguishing factor between e-cigarettes and NRT products.

Summary

- 2.30 For a product to be regarded as a medicine “by function” under Article 1(2) of Directive 2001/83/EC it must be designed to be therapeutic in the treatment or prevention of a disease. The e-cigarette has not been designed to be therapeutic in the treatment or prevention of disease. In fact, its function, design and presentation make it very efficient at maintaining nicotine addiction, which makes it an ideal product for use in harm reduction. Unlike most existing licensed NRTs, which are used to treat nicotine addiction and the related withdrawal symptoms, the e-cigarette is not a medicinal product.

How are e-cigarettes treated in other jurisdictions?

In the EU

Although there is no EU law specific to NCPs, they are effectively regulated under Directive 2001/83 (medicinal products), Directive 93/42/EEC (medical devices) and Directive 2001/95 (general product safety). The European Commission’s *Orientation Note Electronic Cigarettes and EC Legislation*, adds little to the general debate and merely reflects the view taken by the ECJ:

“If a product does not have therapeutic effects, in the recommended dose, it cannot be used with a view to restoring, correcting or modifying physiological functions and hence does not fall under the definition of Article 1(2)(b) of the Directive. The mere fact that it

³²

poses a risk to health cannot alter that conclusion and cannot be the only factor to lead to the classification of the product as medicinal.

This view is also in line with the ruling of the European Court of Justice of 15 November 2007 (C-319/05 - Garlic), where the Court goes a step further and sets out that the definition of medicinal product by function covers products which are genuinely designed to make a medical diagnosis or to restore, correct or modify physiological functions; the product under assessment must have the function of treating or preventing disease (see paragraphs 61, 64 of that judgment).³³

- 2.31 The approach taken across the EU varies. However a number of key jurisdictions do not treat NCPs as medicinal products including Germany (although there are some regional differences in approach) and The Netherlands. This would make a change in the rules largely ineffective as without a Banning Order there would be little to stop sales between Member States and any attempt to do so would run the risk of arguments that they were quantitative restrictions on trade between Member States³⁴.

In the United States

- 2.32 In the United States e-cigarettes falls within the definition of tobacco products, which are defined as “any product made or derived from tobacco that is intended for human consumption”³⁵ and is regulated by the FDA. However the FDA is prohibited from regulating these products as a drug device. In the recent case, *Smoking Everywhere Inc and Sottera Inc, d/b/a NJoy v. U.S. Food and Drug Administration*³⁶, attached as **Annex 2**, the FDA argued that e-cigarettes were in fact a drug device combination, but failed to satisfy the court that these products were a drug device combination within its remit.

- 2.33 The second limb of the EU definition of medicinal product is substantially similar to the U.S. definition of a drug device combination:

“a drug device combination [...] [is] an article intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease. 21 U.S.C. § 321 (h)(2)-(3). Based on the totality of labelling and promotional materials, FDA contends that Smoking Everywhere’s electronic cigarettes either are or are intended to affect the structure or function of the body or are intended for use in the mitigation of disease.”

- 2.34 The Court’s ruling on whether e-cigarettes fall within this definition are therefore a useful reference point when considering how the same product should be interpreted under EU law. The e-cigarettes in this case are also of a substantially similar nature to those sold in the U.K. by Digital. The court examined evidence put forward by the FDA that the e-cigarettes in question were marketed with the intention to alleviate nicotine withdrawal symptoms and found no such evidence. On the contrary the court found ample evidence that they were not:

“The Court has already concluded on the bases of the information before it that the electronic cigarettes marketed by the plaintiffs are not intended for treating the disease of nicotine addiction. [...] Moreover, it would create the absurd result that certain tobacco products - like low tar cigarettes or electronic cigarettes - would be exposed to more

³³ Page 4 n 30 above

³⁴ Under Article 34 TFEU

³⁵ 21 U.S.C. Section 321(rr)(1)

³⁶ See n 8 above

*onerous regulatory burdens for drugs and devices merely because they claim to be healthier alternatives to traditional tobacco products.*³⁷

The Court went on to conclude:

*“[A]bsent substantial evidence of the manufacturer’s objective intent that its electronic cigarettes affect the structure or function of the body in a way distinguishable from ‘customarily marketed’ tobacco products or that its electronic cigarettes have the therapeutic purpose of treating nicotine withdrawal, there is no basis for FDA to treat electronic cigarettes, as they are marketed by the plaintiffs in this case, as a drug-device combination when all they purport to do is offer the same recreational effects as a regular cigarette.”*³⁸

- 2.35 The above case is a clear example of a regulator trying to regulate products outside of its remit, by using existing legislation that was clearly not intended to be used in that manner. A parallel can be drawn between this example and the MHRA’s attempt to draw NCPs within the MA regime on the basis that they are a harm reduction device, even though this argument is clearly outside of the EU definition of medicinal product.
- 2.36 This case is also important in relation to MLX 364, because the evidence put before the court by the FDA, was based on its 4 May 2009 report. The MHRA rely heavily on the evidence in this FDA report in their reasoning in MLX 364, see below for a detailed analysis of the FDA report. Any finding by a court of law that has found against this evidence is therefore highly relevant to the current matter.

³⁷ Pages 25 -26 n 8 above

³⁸ Ibid, p. 26

3 Harm reduction and NRT

- 3.1 The MHRA has failed to construct an adequate argument for the need to regulate NCPs on the grounds of harm reduction. There are three key reasons for this:
1. Harm reduction is not a valid legal ground to regulate medicinal products.
 2. It has not been made sufficiently clear why NCPs are to be included in the MA regime, because they contain nicotine, while tobacco products are exempted. NCPs and cigarettes have the same active ingredient (nicotine) and purpose (recreational nicotine use).
 3. It would create the absurd effect that smoking tobacco would be the least regulated form of nicotine use, even though it is the most dangerous by some margin.
- 3.2 The legal arguments regarding the classification of nicotine as a medicinal product have already been discussed above. However it is important to re-iterate the arguments in the context of harm reduction, because it was not fully elaborated in that section. The argument that the unintentional (or intentional) effect of harm reduction is a medicinal function, does not fall within the legal definition because it is not a product genuinely designed to make a medical diagnosis or to restore, correct or modify physiological functions³⁹. A further reason is that nothing is being treated or cured; the disease that is or would be restored, corrected or modified is nicotine addiction, which is not being served by using NCPs (i.e. the nicotine addiction remains).
- 3.3 It is not at all clear why products containing nicotine have been singled out by the MHRA. Certainly the MHRA cites other factors which may be harmful, erroneously in a number of cases, but the link between the products is that they contain nicotine. However the MHRA explicitly states in MLX 364 that “[w]hile the risks to health from smoking tobacco are well established, a body of evidence is emerging that suggests that nicotine, while addictive, is actually a very safe drug.”⁴⁰ The MHRA has therefore picked the wrong ground upon which to try to regulate these products, in fact the MHRA ought to have chosen the substances that it actually sees as dangerous. Instead we are left with a strange reverse argument that fails on a number of levels, on legal and policy grounds. In fact using the MHRA’s reasoning there is no reason why tobacco products should not be included what-so-ever. They have not been included because it highlights the absurdity of the MHRA’s position.
- 3.4 The decision about how to handle e-cigarettes requires a careful consideration of the overall public health implications of the use of the product. One needs to weigh the clear benefits that this product appears to be having with the possible risks as well as the costs of forcing users of NCPs to go back to conventional cigarette smoking (something which may have substantial public health costs). Regulating NCPs because they contain trace quantities of carcinogens is irrational, because these substances would remain in licensed NCPs, as evidenced by their presence in current licenced NRTs. Such a change in policy could do far more harm than good.
- 3.5 This is a challenging and complicated public health issue. But what it requires is not simplistic, ideological-based thinking. It requires taking a broad view and making a broad assessment of overall public health implications. It also requires objective and meaningful science, not just whether or not carcinogens are detectable in the product (something which was known long before the FDA studied the product and something which is hardly relevant, since NRT products themselves contain detectable levels of carcinogens). It also requires consistency and rationality, and not blind adherence to any particular legal or policy ideology.

³⁹ See n 5 above

⁴⁰ Para. 10 n 3 above

- 3.6 Most importantly, it requires balanced, meaningful, and honest communication with the media and with the public. How meaningful is it to tell the media that e-cigarettes contain carcinogens and not to tell those same reporters that NRT products also contain carcinogens. This misleading position should not be allowed to continue.
- 3.7 A number of important and reputable bodies have highlighted the current problems in the regulation of products containing nicotine. The RCP highlight the following points:
- nicotine products are currently subject to grossly inconsistent regulation;
 - smoked tobacco, which is the most dangerous nicotine product, is freely available and the content and emissions of the product are virtually unregulated;
 - it is now illegal to advertise smoking products in the UK, but cigarettes are available and easily accessible to smokers from a wide range of sources at all times of day and night;
 - NRT products promoted with any health claim come under the control of the MHRA, and are tightly regulated;
 - non-tobacco nicotine products marketed with no health claims are currently unregulated, so their purity and safety are unknown;
 - smokeless tobacco that is not intended to be sucked, including a number of products with significant hazard profiles, is unregulated and can be sold as freely as smoked tobacco; and
 - supply of smokeless tobacco that is intended to be sucked, including the relatively low hazard Swedish snus products, is prohibited in the UK.⁴¹
- 3.8 The RCP conclude the regulatory imbalance perpetuates smoked tobacco as the most freely available, affordable, effective and widely used nicotine delivery product. The current regulatory system therefore strongly favours the most dangerous tobacco products over those that are less hazardous, while imposing the strictest restrictions on medicinal nicotine and this regulatory approach needs to be reformed in the interests of public health.
- 3.9 Digital argue that the solution to this problem is not to perpetuate the inconsistency, but to take direct action on tobacco products and to regulate NCPs in a proportionate manner to the risk they pose to public health. The proposed approach would not be in line with the trend in loosening regulation on NRT products:
- In 1993 NRT was initially virtually exclusively prescription only with quite limited indications for use.
 - At the beginning of the last decade some products became GSL or OTC products.
 - By the end of the last decade all NRTs were available GSL / OTC.
 - In addition product indications have equally expanded dramatically to even now include pre-teen children, pregnant women and patients with serious illnesses.
 - In 2010 harm reduction is added to the indications and MA holders invited to apply for this for all of their NRT products.
- 3.10 It is clear that the wider approach to NRT products containing nicotine is to decrease regulation in line with the danger posed by these products. To start moving the other way is not in the interests of public health and will only result in additional smokers of tobacco cigarettes. At times it even

⁴¹ See n 13 above.

seems as if MLX 364 is arguing against further regulation, in the context of evidence in favour of harm reduction and as an approach beneficial to public health (not regulation):

*“The most recent [body to support harm reduction] (January 2009) is from the BMA Board of Science which has produced a policy position entitled ‘Harm reduction a tobacco free approach supporting those smokers struggling to quit’. They consider that, in terms of harm reduction, **effective alternatives need to be considered that allow an individual to obtain nicotine without being subjected to the risks of smoked tobacco**, and that pure nicotine products currently available as NRT are considerably safer than smoked or smokeless tobacco products.”⁴² (emphasis added).*

- 3.11 Finally with regard to NRT, the long-term evidence is that NRT is not as effective a method for smoking cessation as the MHRA believes. A number of peer review studies in reputable journals, such as the BMJ, have found that the long-term (rather than short-term) quit rate is as low as 7%⁴³.
- 3.12 Combined with the fact that NRT products contain carcinogens criticised in MLX 364 by the MHRA, it seems that the “*clear benefits to risk that has been established for NRT products*”⁴⁴ is not a particularly high threshold and the MHRA have not put forward a convincing enough argument that these products by their function alone require regulation. In fact the real reason why NRT products are regulated is that they are medicinal products by presentation, i.e. they claim to be medicines.

⁴² Para. 11 n 3 above, also please note that NCPs are not considered smokeless tobacco products, because they do not contain tobacco.

⁴³ “A meta-analysis of the efficacy of over-the-counter nicotine replacement” by Hughes, Shiffman, Callas and Zhang, 2002 <http://journals.bmj.com/cgi/reprintform>

^b “Nicotine replacement therapy for long-term smoking cessation: a meta-analysis” by Etter and Stapleton, 2006 www.tobaccocontrol.com

^c “Addictive Behaviours – Relapse to smoking after 1 year of abstinence: A meta-analysis” by Hughes, Peters and Naud, 2008 <http://www.ncbi.nlm.nih.gov/pubmed/18706769>

^d “Effectiveness and safety of nicotine replacement therapy assisted reduction to stop smoking: systematic review and meta-analysis” by Moore, Aveyard, Connock, Wang, Fry-Smith, and Barton, 2009 http://www.bmj.com/cgi/reprint/338/apr02_3/b1024

^e “Nicotine replacement, effective?”, Letter to BMJ published 29 April 2009, Michael Siegel, Professor, Boston University School of Public Health, Boston, MA, BMJ 2009;338:b1730 http://www.bmj.com/cgi/content/extract/338/apr29_1/b1730

⁴⁴ Para 15 n 3 above

4 The existing regulatory framework

- 4.1 NCPs are adequately regulated under the current regime. The current provisions adequately encompass the advent of products such as e-cigarettes and there is therefore no need for further regulation.

The Poisons Act

- 4.2 The Poisons Act provides a framework for the protection of the public from genuinely dangerous products. The Poisons Act prohibits the sale of products classified as poisons, by those without appropriate authorisation, and provides penalties for those who breach these rules as well as immediate removal of such products from sale⁴⁵. Nicotine is a product listed in Part II of the Poisons List and as such certain restrictions apply to it. However it is subject to a complete exemption under the Poisons Rules 1982⁴⁶, attached as **Annex 3**, provided it is in a form or concentration that falls within the exemption, see below:

Nicotine; its salts; its quaternary compounds	<i>Tobacco; in cigarettes, the paper of a cigarette (excluding any part of that paper forming part of or surrounding a filter), where that paper in each cigarette does not have more than the equivalent of 10 milligrams of nicotine; preparations in aerosol dispensers containing not more than 0.2 per cent of nicotine, weight in weight; other liquid preparations, and solid preparations with a soap base, containing not more than 7.5 per cent of nicotine, weight in weight⁴⁷</i>
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- 4.3 This exemption reflects the fact that nicotine is a perfectly legitimate recreational substance and sets out the safe parameters for its use. The exemption is clearly drafted with human consumption in mind, hence the reference to tobacco and cigarettes, and it is broadly drafted to encompass the forms nicotine may take, including solid and aerosol. In short this provision has not been superseded by NCPs, in particular the e-cigarette, and NCPs sit comfortably within the current structure.
- 4.4 The current system adequately protects the public from products that are dangerous. The fact that NCPs fall within the exemption to the Poisons Act indicates that in the eyes of the scientific community the nicotine content of NCPs is not at a level harmful to human health. This conclusion is supported by the MHRA in MLX 364 where there is specific reference to the body of evidence that suggests nicotine is a very safe drug.⁴⁸ Considering the existing framework for the regulation of nicotine at dangerous levels and the body of evidence supporting that it is safe below these levels, the argument to tighten regulation of these products seems to be flawed.

LACORS' concern over the concentration of nicotine in e-cigarettes

- 4.5 A factor that may have contributed to the MHRA publishing MLX 364 is the recent LACORS research, published in a press release in March 2009, contained the following fundamental errors:

“Results of tests commissioned by LACORS on e-cigarettes reveal that these products are currently being sold illegally in the UK. All four e-cigarettes tested had nicotine at

⁴⁵ Section 3(2) Poisons Act 1972

⁴⁶ Reg 8(2) Poisons Rules 1982 (SI 1982/218)

⁴⁷ Ibid Schedule 4 Group 2 Special Exemptions

⁴⁸ See n 40 above

*more than seven percent in solution and therefore are legally required to display 'Highly Toxic' product warning. One refill contained nearly 20 percent nicotine, or 18mg per refill, equivalent to 20 cigarettes.*⁴⁹

- 4.6 This statement is fundamentally incorrect and the MHRA's reasoning is fundamentally flawed and demonstrates its lack of understanding in this matter. For example Digital sell cartridges and 'e-liquid' for e-cigarettes with a nicotine concentration of 18mg/ml, and these do not contain nearly 20% nicotine, in fact they contain roughly 1.8% nicotine i.e. significantly below the threshold in the Poisons Act. Due to discrepancies in the *systeme internationale* (SI) for weights and measures, and the fact that the measurement of a litre does not 'fit' into this system, it is quite common for mistakes to occur in calculations of this sort.
- 4.7 Digital have sent an open letter to LACORS requesting that they retract their press release of 13 May 2009 on the grounds that the scientific evidence underpinning their statement is evidently wrong⁵⁰. However LACORS have not even responded to Digital's letter nor retracted their misleading and incorrect statement.
- 4.8 The SI is the system by which scientific units, and the prefixes which determine multiples or fractions thereof, are defined, e.g. centimetre and kilometre, milligram and kilogram. Although litres share the same prefixes (e.g. centilitre and millilitre) they are not formally incorporated into the SI system because they do not share unit equivalence with other SI units. Due to this lack of equivalence concerning the litre, 1litre (1l) of water (at room temperature and sea-level pressure) weighs 1,000 grams (1,000g = 1kg). Therefore, 1 millilitre (1ml = 1/1000th of a litre) weighs 1 gram (1g), not 1 milligram (1mg = 1/1000th of a gram).
- 4.9 This means that for a solution to contain 20% nicotine, it would have to contain 200mg nicotine per ml. Digital do not believe that any e-cigarette manufacturer has ever produced (or ever would produce) a product at this strength, not least because it would almost certainly kill the user. This would also be a very expensive, because nicotine is the most expensive ingredient in NCPs by some margin. It would certainly not be in a manufacturer's economic interest to sell products at unusually high concentrations.
- 4.10 The level at which nicotine content is classed as 'toxic', and thereby relevant to the Poisons Act, is 7.5%. As demonstrated earlier, this would be applicable to an 'eliquid' or cartridge refill containing 75mg/ml of nicotine. The highest available nicotine liquid/cartridge currently stocked in the UK is 54mg/ml (with the highest cartridge sold by Digital 36mg/ml). Consumers are not recommended to use the substance at this level, but rather to dilute it, which provides a cost-effective option consumers. This is 5.4% nicotine 'eliquid'. Even if a person was to use the 54mg/ml 'eliquid', this would still be well below the level indicated in the Poisons Act. An average user of e-cigarettes may be expected to use 2ml of 'eliquid' per day (108mg) which would still amount to 10% less nicotine than in the maximum recommended dose using a Nicorette Inhaler (twelve 10mg cartridges per day, equating to 120mg).
- 4.11 As discussed above, the scenario raised by LACORS is adequately catered for in existing legislation: if an NCP was found to contain a dangerously high concentration of nicotine it could be removed from the market immediately and the perpetrators prosecuted. However as evidenced by the rebuttal of LACORS' poor research, e-cigarettes do not contain dangerously high levels of nicotine. Finally there have been no instances, to Digital's knowledge, of persons requiring hospital treatment caused by the use of e-cigarettes.

⁴⁹ See n 20 above.

⁵⁰ Email on behalf of e-cigs.co.uk titled 'Global Public Health Alert', regarding misinformation originating from LACORS dated 13 May 2010, attached at **Annex 4**

General product safety legislation and Trading Standards

- 4.12 General product safety legislation applies to NCPs, including e-cigarettes, and the ultimate sanction under Directive 2001/95 enables the regulator, Trading Standards, to withdraw a product from the market where it is established that a product is dangerous to the health and safety of consumers. The implementing legislation the General Product Safety Regulations 2005⁵¹ (the “2005 Regulations”) provide:

“5. General safety requirement

- (1) *No producer shall place a product on the market unless the product is a safe product.*
- (2) *No producer shall offer or agree to place a product on the market or expose or possess a product for placing on the market unless the product is a safe product.*
- (3) *No producer shall offer or agree to supply a product or expose or possess a product for supply unless the product is a safe product.*
- (4) *No producer shall supply a product unless the product is a safe product.*

[...]

7. Other obligations of producers

- (1) *Within the limits of his activities, a producer shall provide consumers with the relevant information to enable them—*
 - (a) *to assess the risks inherent in a product throughout the normal or reasonably foreseeable period of its use, where such risks are not immediately obvious without adequate warnings, and*
 - (b) *to take precautions against those risks.*
- (2) *The presence of warnings does not exempt any person from compliance with the other requirements of these Regulations.*
- (3) *Within the limits of his activities, a producer shall adopt measures commensurate with the characteristics of the products which he supplies to enable him to—*
 - (a) *be informed of the risks which the products might pose, and*
 - (b) *take appropriate action including, where necessary to avoid such risks, withdrawal, adequately and effectively warning consumers as to the risks or, as a last resort, recall.*
- (4) *The measures referred to in paragraph (3) include—*
 - (a) *except where it is not reasonable to do so, an indication by means of the product or its packaging of—*
 - (i) *the name and address of the producer, and*
 - (ii) *the product reference or where applicable the batch of products to which it belongs; and*
 - (b) *where and to the extent that it is reasonable to do so—*
 - (i) *sample testing of marketed products,*
 - (ii) *investigating and if necessary keeping a register of complaints concerning the safety of the product, and*
 - (iii) *keeping distributors informed of the results of such monitoring where a product presents a risk or may present a risk.”*

⁵¹

SI 2005/1803

4.13 There is an obligation on local authorities to enforce the 2005 Regulations. Local authorities are given extensive powers to suspend, recall, or withdraw products⁵². There are also criminal offences for those who contravene the 2005 Regulations, which include large fines and even prison sentences. The above legislation and the associated legislation that is enforced by local authorities and Trading Standards are an effective means to regulate NCPs.

4.14 Although LACORS in their letter titled *Electronic Cigarettes*, dated 3 September 2009, express their concern over the current regulation of e-cigarettes, it is clear from their report that the severe measure of requiring producers to get a MA is not required. LACORS first choice solution would be to extend tobacco legislation to cover e-cigarettes (as is the case in the U.S. and a number of other jurisdictions). The report flags three key areas of concern: advertising and promotion of the product, sales to young people, and product safety. Certainly LACORS first issue advertising and promotion does not add to the argument of MA licensing, not least because if producers were to get an MA they could still advertise. Sales to young people are a genuine concern to the industry, see below the measures taken by sellers of NCPs to self-regulate. LACORS raise the following safety concerns: electrical safety and child resistant packaging. E-cigarettes are battery operated devices and electrical safety concerns are therefore completely unfounded. As to child resistant packaging, see below. LACORS goes on to state:

“There is no recognised standard or safety specific regulations for this product and it is very likely that variations of the electronic cigarette will continue to appear in the market place requiring individual testing to assess compliance with product safety legislation. This will inevitably stretch the resources of these Councils who have importers and distributors within their Council area.

Whilst Councils can continue to apply the General Product Safety Regulations and other safety legislation to these products, in the interest of consumer protection, it is considered that further product specific controls may be required.”

4.15 This statement makes it abundantly clear that the existing regulation is perfectly adequate and that LACORS concerns are based more on the availability of resources than a genuine fear that the public is in real danger from these products. That a product is subject to variation and this may necessitate additional testing for compliance is surely not unique to NCPs and is not a reason to subject NCPs to the MA regime, particularly in light of the legal standard that must be satisfied to necessitate a MA (see above and para 7.10 below).

Current measures of NCP industry

4.16 The vast majority of companies within the e-cigarette Industry in the UK are law-abiding, ethical businesses who have adopted all the measures available to them to safeguard both their customers’ and the general public’s health and safety, particularly since existing regulatory agencies have been unwilling or unable to offer much support or advice to date. A few examples of these self-imposed regulatory restrictions are as follows:

- despite containing well below toxic levels of nicotine, e-cigarettes are usually sold in CHIP-compliant packaging. In addition to child-proof caps on supplies of nicotine-containing cartridges and/or ‘eliquid’ bottles of nicotine liquid, CoSHH hazard warning signs and tactile safety warning triangles are also included on the labelling to alert consumers (including the blind and partially-sighted) to the potential risks associated with handling nicotine;

⁵² Regulations 10 - 16 SI 2005/1083

- explicit warnings are displayed on the majority of legitimate retailers' websites, advising potential customers that e-cigarettes are not smoking cessation devices, but rather offer an alternative to traditional tobacco smoking;
- measures have been put in place by the vast majority of e-cigarette companies to ensure that these products cannot be sold to anyone under the age of 18, and responsible retailers ensure that their packaging/labelling is clearly marked as not for anyone under 18. These precautions are further strengthened by preventative measures at 'checkout', since most companies only permit transactions to be completed with a credit/debit card, or by PayPal®, thus ensuring that customers must be over 18 before they can complete their purchase;
- the same packaging/labelling measures have been taken to protect consumers who are pregnant, and/or any individual who is predisposed to any health problem associated with the use of nicotine, such as cardiovascular problems; and
- manufacturers are making greater efforts to ensure that quality nicotine is being used in e-cigarettes, and many now use pharmaceutical-grade, USP/EP ingredients in the 'eliquid' used in cartridges, or sold in bottles for 'topping up' e-cigarettes.

4.17 These measures are not required nor are they implemented in existing licensed NRT products, which are usually not sold in child-proof packaging, and are increasingly handed out to children in schools. This is another clear indication of the true risk that the MHRA considers these products pose to the general public.

4.18 Despite the belief that current legislation combined with prudent self-regulation are sufficient to safely regulate NCPs, producers of these products are not adverse to sensible proposals for regulatory reform and are keen to work together with LACORS and Trading Standards toward regulation of these products that will benefit the public: an end that will not be met by the removal of these products from the market, nor would this approach be in line with the regulation of NCPs in other jurisdictions. In fact the reclassification of NCPs as a medicinal product in the U.K. would be likely to have far ranging consequences on the regulation of NCPs in other European jurisdictions, due to the influential nature of any U.K. decision based on legal grounds. As such, it is vital that the MHRA takes great care before rushing into a course of action not adequately substantiated by scientific evidence or firmly grounded on legal principles.

5 Safety

FDA press release, 22 May 2009

5.1 In the United States, the FDA undertook its own limited testing of e-cigarettes, which led the FDA to publish a press release announcing their findings⁵³, and warning of the dangers posed by e-cigarettes. Unfortunately, this told only part of the story: the truth is that similar levels of TSNAs are found in existing licensed NRT products, and they are a natural result of using nicotine, which is a tobacco derivative. Furthermore, in both existing licensed NRT products, and in e-cigarettes, the levels of TSNAs are so low as to pose little or no risk to consumers.

5.2 The FDA study reported the presence of four TSNAs – N-nitrosornicotine (“NNN”), N-nitrosoanabasine (“NAB”), N-nitrosoanatabine (NAT) and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butaone (“NNK”) Of the four TSNAs noted by the FDA study, only NAT was found in the NJOY vapor and only at trace levels. NAT has been shown through published scientific studies to be nontoxic and noncarcinogenic. Ben Thomas, Ph.D., a well-respected consultant with 35 years' experience in toxicology, pathology and risk mitigation concluded that “[b]ased on my review of scientific literature, NAT is not toxic and not carcinogenic, and based on the vapour analysis, it is my conclusion that TSNAs do not pose a health risk to the users of the e-cigarettes distributed by NJOY.” The FDA report has been criticised by public health experts and the scientific validity of the report questioned. Dr Thomas, in conjunction with premier independent consulting laboratory ANALYZE, conducted an analysis of the same NJoy cartridges as the FDA, attached as **Annex 5**. The FDA's analysis was also roundly condemned in a report produced by Exponent, attached as **Annex 6**, which concluded:

- *“The report failed to present standard protocols for proper study design with regards to the testing of the referenced control device, documenting the number of samples tested either within or across tests, or presenting statistical analyses when quantifiable results were obtained.*
- *The chemical content of similar nicotine-containing FDA-approved products was not completely described with respect to the presence of tobacco-specific nitrosamines (TSNAs) and other tobacco-associated impurities that have also been found in nicotine replacement therapy (NRT) devices at similar, if not higher, levels.*
- *In the lots that were tested by the FDA, none of the key chemicals of concern in this study such as TSNAs and tobacco-associated impurities were able to be quantifiably measured in the liquid of NJOY's cartridges because they were all below the limits of quantification (LOQ).*
- *All of the tobacco-associated impurities found in the NJOY products were **“present but at less than the level of the Nicotrol® Inhaler [manufacturer] specification”** according to the FDA report.*
- *There is no indication in the published scientific literature that cotinine or β-nicotyrine are carcinogenic or have toxicity ratings of concern. These were the only tobacco-associated impurities found in trace levels in the vapour phase of (some of) NJOY's products.*
- *The report does not reflect the actual dose of nicotine delivered to the user from the “control” Nicotrol® Inhaler device when used as recommended by the manufacturer (6–16 cartridges/day or 24–64 mg of nicotine, 50 mcg/100*

⁵³

FDA 22 May 2009 press release. Available at:
<http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm173222.htm>

mL puff). By comparison, NJOY devices delivered 46 mcg/100 mL in the highest-strength cartridge tested, according to the FDA report.

- *Data presented in the report does not adequately support the opinion that users of NJOY products would actually be exposed to TSNA and tobacco-specific impurities in the vapour phase during normal device use; and if exposed, that those levels would be a health concern as compared to other FDA-approved products.*⁵⁴

- 5.3 In its July 22, 2009 press conference, FDA adopted the position that since the safety of e-cigarettes has not been proven in a clinical trial, FDA will presume that e-cigarettes are as hazardous as conventional cigarettes, and possibly even more hazardous. FDA cited results of its own laboratory studies which showed trace contamination with carcinogenic substances as evidence in favour of this view, without mentioning that the contaminants and levels of contamination are similar to those of FDA approved NRT products, and orders of magnitude less than conventional cigarettes.
- 5.4 A certificate of analysis of Digital's nicotine containing fluid from Scientific Analysis Laboratories⁵⁵, a UKAS⁵⁶ and MCERTS accredited laboratory and an LPD Lab Services Test Report, is attached at **Annex 7**. The certificate shows that the nicotine-containing fluid contains a minuscule number of elements alongside the nicotine, and at often below LOQ levels, especially when compared with the potentially toxic additives in tobacco cigarettes. Furthermore, the levels of nitrosamines and tobacco by-product toxins in Digital's product range are no more than those found in the NJoy samples analysed, and no more than in existing, licensed NRT products. The FDA's evidence was also put before Judge R J Leon, who did not find it a compelling case for protection of public health⁵⁷.
- 5.5 The FDA did not adequately emphasise that NRT have been found to have detectable levels of tobacco-specific nitrosamines, including NNK and NNN⁵⁸. Both of these chemicals are consistently carcinogenic in laboratory animals and are widely recognized as carcinogens present in tobacco products. The carcinogen NNK was found to be present at a concentration of 0.008 micrograms per patch in NicoDerm CQ and NNN was found to be present at a concentration of 0.002 micrograms per piece in Nicorette. On this basis it seems that on the FDA's analysis NRT products should also be removed from the market as they expose consumers to known tobacco-specific carcinogens, as of course should cigarettes, which contain many times the amount found in NRT and NCP products. For example, Nicorette gum was found to contain 0.002 µg/g of NNN compared to 2.8 µg/g of NNN in Marlboro Light cigarettes (140,000% as much).
- 5.6 The laboratory data provided by the FDA is conspicuously missing a control substance for the tests for carcinogens. The nicotine inhaler was used as a control specimen for the nicotine testing, but not subjected to testing for carcinogens. The FDA report states that: "Nicotrol Inhaler was used as a control for some test methods." In a scientific analysis of similar products it seems inconceivable that the FDA did not attempt to demonstrate a key argument: that e-cigarettes have detectable levels of carcinogens, whereas NRT products do not. This is either a serious failing in

⁵⁴ Exponent (2009) Technical Memorandum Technical Review and Analysis of FDA Report: "Evaluation of e-cigarettes", July 30, 2009, p. 1

⁵⁵ Scientific Analysis Laboratories describe themselves as "an *independent* laboratory specialising in *accredited analytical services* for the environmental, safety, chemical, petrochemical and manufacturing sectors of industry throughout the UK and world wide." [Source: <http://www.salltd.co.uk/>]

⁵⁶ Please note that the tests conducted for Digital were not UKAS accredited.

⁵⁷ See n 8 above.

⁵⁸ Stepanov, I. Jensen, J. Hatsukami, D. & Hecht, S.S. (2005) "Tobacco-specific nitrosamines in new tobacco products", *Nicotine & Tobacco Research*, Volume 8, Number 2 (April 2006), pp. 309 - 313. The article is attached in full at **Annex 8**.

the study or indication of the FDA's bias. Either way it questions the scientific value and reliability of the FDA's press release.

- 5.7 The essential question that needs to be asked is whether or not e-cigarettes are safer than conventional cigarettes? If they are, and if they reduce exposure to highly toxic cigarettes, then they could be a huge benefit to the public's health.

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- 5.8 Paragraph 16 MLX 364 states that "unexpectedly high doses of nicotine could produce adverse effects, particularly in some vulnerable patient groups such as those with cardiovascular disease." This is not a fact borne out by the WG minutes, these minutes are included on the MHRA website along with the consultation document⁵⁹, which states "*From the data available for patients without pre-existing cardiovascular disease there was little evidence that nicotine was a risk factor for this, however, the WG highlighted the absence of long term safety data in patients with cardiovascular disease*"⁶⁰. The WG go on to make the following statement regarding the safety of NRT:

"5.3 The WG noted that there was no evidence of an increase in cardiovascular or Myocardial Infarction (MI) events or in deaths related to NRT use. Although not submitted with the application, the WG noted that the SCENIHR report Health Effects of Smokeless tobacco Products (February 2008) was highly relevant. This study evaluated, among other products, SNUS (a moist snuff from Sweden). The study did not show an increased risk of cardiovascular disease, nor an increased risk of MI. When MI did occur in the study, however, it was more likely to be fatal. The study showed a small increase in the risk of pancreatic cancer. The WG concluded that there was a spectrum of evidence which supported the safety of NRT in long term use and that the Swedish data supported this conclusion.

*5.4 The WG also considered the safety of concomitant use of NRT and smoking. There was evidence of an increase in blood nicotine levels compared to smoking alone but this was balanced against the lower intake of other toxins contained in tobacco smoke, such as carbon monoxide. There was some evidence to suggest smokers regulated their own nicotine levels, just as they do when smoking tobacco alone. The WG therefore concluded that the overall effect of reducing the consumption of smoked tobacco was beneficial."*⁶¹

WHO recommendation

- 5.9 The MHRA cite the WHO (Draft Abbreviated Advisory of the WHO Study Group on Tobacco Product Regulation – September 2008) However it is clear from this report that it fails to adequately recognise the potential for harm reduction. This shows the report is out of touch with current medical thinking and should therefore be disregarded. Research conducted by Professor Michael Siegel, Dr Joel Nitzkin and the AAPHP, the Royal College of Physicians Tobacco Advisory Group, and a number of other sources conclude that the electronic cigarette should be given an opportunity to provide a realistic and attractive alternative to tobacco smoking. All these experts concur that irrational and prohibitive regulation can only cause harm, not reduce it.

LACORS press release

⁵⁹ <http://www.mhra.gov.uk/Publications/Consultations/Medicinesconsultations/MLXs/CON065617> [as at 27 April 2010]

⁶⁰ Extracts from the minutes of the meeting of the Working Group on Harm Reduction & Nicotine Replacement Therapy held on 14 October 2009. Available at: <http://www.mhra.gov.uk/Publications/Consultations/Medicinesconsultations/MLXs/CON065617> [as at 27 April 2010]

⁶¹ Extracts from the minutes of the meeting of the Working Group on Harm Reduction & Nicotine Replacement Therapy held on 14 October 2009. Available at: <http://www.mhra.gov.uk/Publications/Consultations/Medicinesconsultations/MLXs/CON065617> [as at 27 April 2010]

- 5.10 Another source relied on with regard to the safety of e-cigarettes was the LACORS press release discussed at paragraphs 4.5 - 4.10 above. As discussed, the evidence provided by LACORS as to e-cigarettes' danger to public health is completely unfounded.

Propylene Glycol

- 5.11 The following information is summarised from the United Nations Environment Programmes Strategic Approach to International Chemicals Management ("SAICM") report on propylene glycol ("PG").⁶²

Exposure

- 5.12 PG production capacity in the US was 1312 million pounds (596 kilotonnes) in 1998. Domestic demand was 1050 million pounds (477 kilotonnes). PG is used as an ingredient in cosmetics at concentrations of <0.1% to >50%. Approximately 4000 cosmetic products contained PG in 1994. Uses of PG, with percent of demand, are: unsaturated polyester resins, 26 percent; antifreeze and de-icing fluids, 22 percent; food, drug and cosmetics uses, 18 percent; liquid detergents, 11 percent; functional fluids (cosmetic creams, paints, inks, specialty anti-freeze, de-icing lubricants), 4 percent; pet foods, 3 percent; paints and coatings, 5 percent; tobacco, 3 percent; miscellaneous, including plasticizer use, 8 percent.

- 5.13 Potential worker exposure to propylene glycol is estimated to be 1,748,454 workers with a projection that 98% of potential exposures occur with trade name products containing propylene glycol, and the balance in the production of the chemical⁶³. Dermal exposure is given as the most significant route of exposure in occupational settings. In the commercial service and consumer settings use as a functional fluid (paints, de-icing, cosmetic creams) presents a potential for inhalation exposure in addition to dermal exposure. In the consumer setting, exposure by ingestion is a result of the approved use of propylene glycol in food, tobacco and pharmaceutical products by the US Food and Drug Administration (FDA)⁶⁴. Dermal exposure, and to a lesser degree inhalation exposure are to be expected where propylene glycol is formulated into cosmetic products.

Toxicity studies

a) Acute toxicity

- 5.14 The acute oral toxicity of propylene glycol has been investigated extensively over the past 60 years in a range of species, including rats, mice, guinea pigs, rabbits, and dogs⁶⁵. The lowest oral LD50 values range between 18 and 24.9 grams (5 relevant and different species). Representative data indicate oral LD50 values of 24900 mg/kg bw in the mouse, 22000 mg/kg bw in the rat, 18000 mg/kg bw in the rabbit, 19700 mg/kg bw in guinea pig and 20000 mg/kg bw in the dog. The acute dermal toxicity of propylene glycol in rabbits was 20800 mg/kg bw (20.8 grams⁶⁶). Overall propylene glycol is not acutely harmful after ingestion or skin contact. There is no evidence to suggest that propylene glycol has any carcinogenic potential. In conclusion, propylene glycol is not a reproductive or developmental toxicant.

⁶² United Nations Environment Programmes Strategic Approach to International Chemicals Management ("SAICM") (2001), 1-2 Dihydroxypropane CAS: 57-55-6 SIDS Initial Assessment Report for 11th SIAM (USA, January 23-26, 2001) <http://www.chem.unep.ch/irptc/sids/OECD/SIDS/57-55-6.pdf>

⁶³ SAICM (Ibid.) cite as its source NIOSH, the National Occupational Exposure Survey (NOES), 1989

⁶⁴ SAICM (Ibid.) cite as its source FDA, GRAS list, 20 CFR 184.1666 and 21CFR 582.4666 4/1/93

⁶⁵ SAICM (Ibid.) cite the summary by Laug et al. , 1939; Ruddick, 1972; Clark et al., 1979)

⁶⁶ SAICM (Ibid.) cite as its source NPIRI, 1974

b) Human health assessment

- 5.15 Propylene glycol does not present an acute, chronic, reproductive, or developmental hazard. Acute toxicity is very low, with LD50 values exceeding 19000 mg/kg after ingestion or skin contact. It is not a skin or eye irritant, and does not cause sensitization. The weight of the evidence indicates that it is not genotoxic in vitro or in vivo. Adequate long-term feeding studies are available which indicate that it does not represent a cancer hazard.

6 Efficacy and quality

6.1 In terms of efficacy, surely its true measure is whether the end user can receive sufficient nicotine to control (or sustain) their addiction. Just as a smoker who wants more nicotine will smoke more, so a user of an electronic cigarette will simply use more of the product until the desired level is reached. Exactly the same is true of the Nicorette range. Furthermore, it is worth noting that market forces will play a part in sales of any kind, including sales of medicinal and/or therapeutic products as well as in sales of general consumer products. This can serve to assist in confirming or denying efficacy: consumers will not buy products if they do not work, and yet the e-cigarette business is growing exponentially because customers are finding the products to be an effective and satisfying alternative to smoking tobacco. It is also the case that if a product is not of a sufficiently high standard of quality, that product simply will not sell. Digital currently serve a customer base of approximately 6,000 UK residents, including many regular customers placing repeat orders for their products.

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6.2 The MHRA's key concern with the efficacy of NCPs is that ineffective products may cause users who try to use them to quit smoking (against clear instructions on the products themselves) and fail, may deter future attempts to try to quit smoking. In relation to this point the MHRA state that:

“As the quality and efficacy of these unlicensed products cannot be guaranteed, users getting sub-therapeutic doses of nicotine may consider that all nicotine-containing products (including medicinal forms) do not work, and so make it more difficult for them to make a successful quit attempt. If as a result of the removal of unlicensed NCPs/licensing of these products as medicines, smokers choose to use a licensed NRT product instead of an unlicensed NCP there could potentially be an increased number of successful quit attempts as a result of the public having access to products that have been assessed for quality and efficacy[.]”⁶⁷

6.3 The WG did not come to a similar conclusion as the MHRA and this is another example of the MHRA making completely unsubstantiated claims.

“Will cutting down undermine a future quit attempt?”

The WG agreed that there was a lack of data as to whether cutting down could undermine a future quit attempt, although noted that the available evidence pointed towards a reduction in smoking being beneficial to future quit attempts. The WG noted that new Quality and Outcome Framework (QOF) targets resulted in GP practices being rewarded according to how many patients they helped to quit smoking, rather than those cutting down. It was noted, however, that there was a NICE consultation on QOF targets at the time the WG met.”⁶⁸

6.4 As such we also request that the above statement made by the MHRA be disregarded.

Other evidence

6.5 At Annex A of MLX 364 the MHRA cite evidence showing a lack of efficacy of NCP products. Although Digital does not intend to comment on products other than e-cigarettes, it seems that the MHRA's evidence in this area is inadequate, the reports concern products no longer stocked in the U.K. and the dates of the articles are 1989, 1993 and 1998, which may be acceptable in studies into medical factors but in terms of product efficacy is far too historical to be relevant.

⁶⁷ Para. 21 n 3 above

⁶⁸ Para 5.8 n 15 above

7 Impact assessment

7.1 The MHRA has not carried out a comprehensive risk assessment for MLX 364. The report relies on the scientific analysis of other agencies, primarily the FDA. There seems to have been no effort to undertake any kind of independent scientific study by the MHRA, even LACORS conducted their own testing (albeit badly). The importance of comprehensive risk assessments was highlighted by the report of Philip Hampton titled *Reducing administrative burdens: effective inspection and enforcement*⁶⁹:

“The review believes it should be possible to achieve greater excellence in regulatory outcomes – but to do so substantially more efficiently, by:

- *entrenching the principle of risk assessment throughout the regulatory system, so that the burden of enforcement falls most on highest-risk businesses, and least on those with the best records of compliance; [and]*

[...]

- *making much more use of advice, again applying the principle of risk assessment[.]”*

7.2 The consultation has also been held during an election period against Cabinet Office election guidance, as admitted by the MHRA itself⁷⁰. The MHRA in postponing the stakeholder meeting is conceding that it is not allowed to consult whatsoever during an election period. When the consultation was initiated in February 2010, an election would inevitably fall between that date and the 10 May 2010, because the last legal date for the election was June 2010. The action of the MHRA in this regard may have prejudiced Digital and jeopardised the consultation, by postponing an important stakeholder meeting.

7.3 The measure proposed by the MHRA is not proportionate to the risk posed by NCPs and in proposing to change the rules 21 days following the end of the consultation are not complying with this principal. There are strict legal obligations to conduct a consultation in an appropriate manner, Wade and Forsyth point out that::

“Whether or not consultation is a legal requirement, once ‘embarked upon it must be carried out properly’. This requires consultation while the proposals are still in formative stage, adequate reasons for the proposals to be given so that those consulted might give an ‘intelligent response’, adequate time to do so and proper consideration of those responses.”⁷¹

7.4 Digital believes it has a legitimate expectation based on the established practice that changes to law and policy are made with adequate time to allow those affected to comply with the new law, in the absence of an overriding public interest.⁷² Digital is also entitled to be treated fairly both during the consultation process and, should it be successful, afterwards. Failure to recognise these factors could lead to a court finding that the MHRA’s conduct amounts to ‘grossly unfair administration’.

7.5 For a producer of NCPs to obtain a MA would take up to two years and would cost tens of thousands of pounds. The MHRA simply quotes its own fees in this regard; by underplaying the

⁶⁹ (2005) HM Treasury, March 2005

⁷⁰ Email from Clare Hedges of the MHRA dated 16 April 2010, attached at **Annex 9**

⁷¹ Wade, H. W. R. & Forsyth C. F. (2004) *Administrative Law* (9th ed.) Oxford: Oxford University Press, p. 897

⁷² *Ibid*, p. 504

cost of obtaining a MA the MHRA are actively seeking to mislead those who engage in the consultation.

“There will also be an annual cost for maintaining an MA, which includes an annual periodic fee of £452, inspection fees at a daily rate of £2562 (assuming an average inspection visit of 2 days), and a GSL annual periodic fee of £424. There may also be a consultancy fee for putting the application together and then on a yearly basis for conducting regulatory affairs/pharmacovigilance on behalf of the manufacturer. We have assumed an hourly rate of £60 and that an average of 5 days work per year will be needed. There will also be additional administration costs to comply with the regulation. These have not been estimated here.”

7.6 Considering the true cost, even by conservative estimates, is likely to be in the region of tens of thousands of pounds, there are grounds that MLX 364 does not comply with a number of principals of administrative law. To expect current producers to obtain a MA within a 12 week time-span (when these products have been used safely for a number of years) or cease selling is not a reasonable or proportionate proposal. Especially when the MHRA has put forward no evidence that these products are any more harmful than existing NRT products, or that they are harmful to human beings in any measurable manner. It is argued that to implement the MHRA's proposed Option 1, would breach the principals of natural justice: adequate time to comply with the change has not be offered, nor would the move be proportionate or reasonable. As such a remedy would be available by initiating a judicial review process, whereby injunctive relief or damages could be sought.

7.7 The proposal leaves little option, but for the existing manufacturers/distributors of NCPs to be removed from the market. The affect that this proposal has on these small businesses has not been adequately quantified, nor has it been represented in the consultation document. This proposal would favour large pharmaceutical companies and would appreciably affect competition in the market.

7.8 The MHRA goes on to quantify the cost saving if the proposal went ahead. This section of MLX 364, is barely worth consideration considering its largely unquantifiable assumptions:

“If as a result of the removal of unlicensed NCPs/licensing of these products as medicines, smokers choose to use a licensed NRT product instead of an unlicensed NCP there could potentially be an increased number of successful quit attempts as a result of the public having access to products that have been assessed for quality and efficacy and by ensuring they also have access to high quality patient information to support their effective use and to highlight the risks of continued smoking. If smokers go on to quit this will have a large public health benefit. This benefit can be calculated as follows. The current DH appraisal value for cost benefit analysis is £60,000 per quality adjusted life year gained, in this case saved as a result of quitting smoking. It is estimated from the British Doctor's study (Doll et al, 2004, BMJ) and Godfrey et al (Addiction, 2005) that people who permanently quit smoking gain an average of 3.59 life years. It is assumed that the proposed regulation will bring about additional smokers who successfully quit using a licensed NRT product. The annex gives the details of the additional quitters using licensed NRT products, with figures from the NHS Information Centre and a Yudkin et al (BMJ, 2003) paper. The calculation estimates that 1,312 individuals will quit using licensed NRT products, which gives a monetary value of the public health benefit of this regulation at $£60,000 \times 3.59 \times 1,312 = £282,511,747.$ ”

7.9 This statement is objectionable on two grounds. Firstly it does not adequately cover the use of NCPs, assuming all users wish to quit smoking, whereas most customers use it as an alternative to smoking. Secondly the values used appear to have no grounding in fact. There is no reasonable justification as to why 1312 people will quit. The Annex referred to uses data from an

existing study, using current NRT products⁷³. There is no justification as to how this figure applies to NCPs, which are not used as NRT in the majority of cases. Therefore the number of users trying to quit smoking with NCPs seems to have been plucked 'out of thin air'. It does not factor in those who cease smoking using unlicensed products. Neither does it explain why existing NRT products cannot adequately service the needs of those who choose to quit. It also seems to rely to some extent on the MHRA's argument that failed quit attempts negatively affect future quit attempts, which was dismissed above⁷⁴. The truth of the matter is that bringing NCPs within the MA regime would not appreciably affect the number of people who quit smoking. It may, on the contrary, reduce the number of people who quit smoking, because some users use these products for smoking cessation (against explicit instructions), rather than using NRT products.

- 7.10 Furthermore the argument for regulation fails to adequately cover the risk of non-UK internet sales, which would completely undermine the efficacy of the proposal. It would counter the purpose of the proposal by driving people to buy products, not subject to UK general product legislation, on-line. This serious consequence is afforded only four lines in MLX 364:

"Key Assumptions/Sensitivities/Risks

*It is assumed that 50% of NCPs will become licensed. A potential risk is the sale of the NCPs from foreign market advertised on the internet as there are virtually no controls on importation for personal use and so it is not possible to prevent products advertised on non-UK websites being sold and supplied to the UK, unless we had a Banning Order in place."*⁷⁵

- 7.11 This is another example of the unprofessional approach taken by the MHRA.
- 7.12 Finally it is important to highlight the significance of the MA regime and the high threshold established in Community law required to justify such a move. The ECJ in Case C-319/05, stated that "[t]he issuing of a marketing authorisation under Article 8 of Directive 2001/83 is subject to particularly strict requirements, and the obligation to obtain such an authorisation before being able to market the product concerned in the territory of the Member State cannot be regarded as being in accordance with the principle of proportionality unless it is actually necessary to safeguard public health."⁷⁶ The MHRA have not satisfied this standard and the introduction of this measure could be found to be a measure having equivalent effect to a quantitative restriction within the meaning of Article 34 of the Treaty for the Functioning of the European Union ("TFEU").

⁷³ "The Information Centre for Health and Social Care published the statistics of people using Stop Smoking Services in October 2009 (www.ic.nhs.uk/statistics-and-data-collections/health-and-lifestyles/nhs-stop-smoking-services). 163,946 individuals set a date between April and June 2009, which gives an assumed annual figure of 655,784. The IC states that 79% of quitters used NRT, some 524,627 individuals. A literature review in analysis by the Department of Health included a Yudkin et al ('Abstinence from smoking eight years after participation in randomised controlled trial of nicotine patch', 2003, *BMJ*, 327, pp. 28-29) paper, which found that 5% of smokers who quit using NRT remained quit after 8 years, and are assumed quit thereafter. Given the named products will be licensed and approved for safety, efficacy and quality; it is assumed that a similar success rate will be the case for users of these products. The number of quitters that can be estimated to use the newly regulated products alone is assumed to be 5% of the above NRT figure, some 26,231 individuals. Using Yudkin's success rate, this gives 1,312 people successfully quitting using the newly regulated products, giving a public health benefit in monetary terms ranging from £235,426,456 - £282,511,747 (£50,000 - £60,000 x 3.59 x 1,312)." [p. 27 to MLX 364]

⁷⁴ See para 6.3 above

⁷⁵ P. 18 n 3 above

⁷⁶ Para 89 n 3 above

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