Adverse-event management and reporting for electronic cigarettes (e-cigarettes)

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The Tobacco Products Directive 2014/14/EU controlling nicotine-containing products has been implementing regulatory control over most electronic cigarettes (e-cigarettes) and related nicotine-containing and non-nicotine-containing consumer products. Since their introduction, e-cigarettes have been debated extensively in the scientific and political community. Sidestepping much of the controversy, this paper focuses on the directive's requirement on reporting of 'adverse health effects' which pharmacists would recognise as adverse drug reporting (ADR).

ADR is implemented and supported by the national competent agency which in the case of the UK is The Medicines and Healthcare products Regulatory Agency and overarching in Europe is the European Medicines Agency (EMA).

As a category, e-cigarettes are different from a healthcare perspective—they are not classed in the traditional categories of regulated items that we are all familiar with such as 'medicine', 'food', 'cosmetic' or 'supplements'. However, e-cigarettes are nicotine-containing products.

Except for nicotine replacement therapy and varenicline, which have a much longer proven history of effectiveness, the e-cigarette is the 'pariah' of the healthcare community. Scientifically, we know that the human body produces endogenous ubiquitous nicotine[1 2] that acts on nicotinic receptors differently in different developmental stages of the human growth and maturation process.[3] It also is the main pathway that smokers hijack to get the satisfaction from smoking. We know that nicotine exposure itself is correlated with increased risk of cancers in adults. In the fetus, infants and adolescents, nicotine exposure (along with other carcinogens and mutagens in cigarette smoke) results in low birth weight,[4] and neurological and developmental delays[5] are among many other negative outcomes. As a consequence, most healthcare professionals would possibly be biased and *not* see the e-cigarette as a true cessation aid or replacement therapy. I want to consider the consequence of this professional bias.

The main one: surrounding ADR. Often, because of the physical device and the nature of this inherent bias, we may think of e-cigarettes as a non-medicinal consumer item. We may consider any adverse event to be consequent to faulty product or faulty use by the customer (or patient). With this mental framework, it is easy to forget that nicotine is pharmacologically active! Irrespective of the potential inaccuracies in labelling, e-cigarettes are very much 'not normal' for the human physiology.

I hypothesise that this bias is particularly played out for e-cigarettes and is supported by significant under-reporting of this particular category versus other medicinal categories (which also we know are under-reported at a rate of anywhere between 59% and 100%[6]). In the UK, there were only 72 spontaneous reports of e-cigarettes (period covering 1 January 2010 to 10 September 2018) which had two fatalities. To give you a comparison: for aspirin, the total number of ADRs were 1663 (covering a period from 2010 to 31 July 2018).

The directive specifies that '*In order to ensure appropriate market surveillance by Member States, it is necessary that manufacturers, importers and distributors operate an appropriate system for monitoring and recording suspected adverse effects and inform the competent authorities about such effects so that appropriate action can be taken. It is warranted to provide for a safeguard clause that would allow Member States to take action to address serious risks to public health.*' This allows for economically active market participants like manufacturers to maintain such records. It is unclear how they may classify a customer complaint which incorporates an ADR and to what degree of detail. It is also unclear if such participants engender a culture of safety and actively encourage ADR from potential customers. This may be compounded by the 'cool' culture of e-cigarette users who may consider such reporting to be unfashionable.

Fortunately, the directive asks competent authority to collate publicly reported adverse events. The provision further allows: '*In the case … where a competent authority ascertains or has reasonable grounds to believe that specific electronic cigarettes or refill containers, …could present a serious risk to human health, it may take appropriate provisional measures.*' These provisional measures can include suspending the product licence rendering their sale unlawful. However, the product licence cannot be suspended if the EMA does not have the data to support such a decision as submitted by national competent agencies.

Another complication of patient-reported side effects is that they are difficult to distinguish sometimes from the side effects of smoking. Smoking or vaping may produce respiratory side effects which may be difficult to attribute to a cigarette or an e-cigarette, especially in the case of dual use (smoking and vaping). Also smoker's self-identity may be linked to some ADRs that become incorporated into their activities of daily living—for example, early-morning sputum productive cough. In this backdrop, it is difficult for them to notice adverse effects that a non-smoker might notice.

Given these products are relatively recently popularised, it can be safely assumed that the full side effect profile is not fully known. Consequently, spontaneous reporting of suspected side effects is of particular importance, in line with the black triangle to identify medicines under additional monitoring reporting standard which requires *all* suspected adverse reactions to be reported EU wide.

Pharmacovigilance is an activity that has international significance. Pharmacists are partners in pharmacovigilance, in drug regulation, in clinical practice and pharmacovigilance in international health.[7] The WHO recognises that pharmacists engage in public health promotion via health-promotion campaigns, locally and nationally, on a wide range of health-related topics, and particularly on drug-related topics (eg, rational use of drugs, alcohol abuse, tobacco use, discouragement of drug use during pregnancy, organic solvent abuse, poison prevention) or topics concerned with other health problems (diarrhoeal diseases, tuberculosis, leprosy, HIV infection/AIDS) and family planning.[8]

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If nothing, this piece is aimed at raising awareness about pharmacists' responsibility (possibly obligation) for reporting ADRs via their national competent agencies—data which are fed into the EMA and affect marketing authorisations across Europe (eg, the Yellow Card Scheme in the UK).

Competing interests None declared.

Provenance and peer review Not commissioned; internally peer reviewed.

To cite Barrett R. *Eur J Hosp Pharm* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/ejhpharm-2018-001747

Eur J Hosp Pharm 2018;**0**:1–2. doi:10.1136/ejhpharm-2018-001747

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