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Electronic nicotine delivery systems: a research agenda

Jean-François Etter,¹ Chris Bullen,² Andreas D Flouris,³ Murray Laugesen,⁴ Thomas Eissenberg⁵

Electronic nicotine delivery systems (ENDS, also called electronic cigarettes or e-cigarettes) are marketed to deliver nicotine and sometimes other substances by inhalation. Some tobacco smokers report that they used ENDS as a smoking cessation aid. Whether sold as tobacco products or drug delivery devices, these products need to be regulated, and thus far, across countries and states, there has been a wide range of regulatory responses ranging from no regulation to complete bans. The empirical basis for these regulatory decisions is uncertain, and more research on ENDS must be conducted in order to ensure that the decisions of regulators, health care providers and consumers are based on science. However, there is a dearth of scientific research on these products, including safety, abuse liability and efficacy for smoking cessation. The authors, who cover a broad range of scientific expertise, from basic science to public health, suggest research priorities for non-clinical, clinical and public health studies. They conclude that the first priority is to characterize the safety profile of these products, including in long-term users. If these products are demonstrated to be safe, their efficacy as smoking cessation aids should then be tested in appropriately designed trials. Until these studies are conducted, continued marketing constitutes an uncontrolled experiment and the primary outcome measure, poorly assessed, is user health. Potentially, this research effort, contributing to the safety and efficacy of new smoking cessation devices and to the withdrawal of dangerous products, could save many lives.

INTRODUCTION

New products, electronic nicotine delivery systems (ENDS) also known as electronic cigarettes (or e-cigarettes), have recently become popular in spite of a dearth of research on their safety and efficacy.¹⁻³ ENDS look like cigarettes, but do not burn tobacco. Instead they produce a vapour from a battery-powered heater and cartridges.^{4 5} Depending on the brand, cartridges usually contain nicotine, humectants to produce the vapour (eg, propylene glycol or glycerol) and flavours (eg, tobacco, mint, fruit, chocolate). Some brands contain other medications (eg, rimonabant, amino-tadalafil).⁶ In addition to the delivery of nicotine, the visual, sensory and behavioural aspects of these devices are similar to

tobacco cigarettes and may explain why they decrease craving and tobacco withdrawal symptoms,⁷⁻⁹ are perceived by users as effective for smoking cessation,¹ or are used as substitutes for cigarettes.^{10 11}

However, there is little objective information concerning the safety, abuse potential and efficacy of these products.¹² Other concerns have been expressed, including that some flavours may appeal to children, that ENDS may become a gateway to smoking or to nicotine addiction, that they undermine smoke-free laws, delay a smoker's decision to quit or might be used in conjunction with drug misuse.^{2 3 13 14} As with any other drug delivery device, these products need to be regulated.^{13 15} Thus far, there has been a wide range of regulatory responses ranging from no regulation to complete bans. WHO's Study Group on Tobacco Product Regulation advised a precautionary approach to ENDS,¹⁶ and with few exceptions (eg, a recent court decision barred the US Food and Drug Administration (FDA) from regulating ENDS as drugs),¹⁷ most national regulatory agencies have also adopted a similar stance.¹² The empirical basis for these regulatory decisions is uncertain, and more research on ENDS must be conducted in order to ensure that the decisions of regulators, healthcare providers and consumers are based on science.

The aim of this paper is to identify priorities for non-clinical, clinical and public health research on ENDS (box 1). We cover a broad range of scientific expertise, from basic science to public health.

PRECONDITIONS REQUIRED FOR RESEARCH ON ENDS

Several issues should be considered first: product purpose, standardisation and regulation. With regard to purpose, many users report using ENDS to reduce or stop smoking, to substitute for cigarettes in smoke-free environments, to inhale various medications, to save money, because these products are perceived to be safer than tobacco, or to experiment with a new product.^{1 11 18} Because ENDS are frequently described as smoking cessation aids,^{1 11} we have examined them mainly with this purpose in mind.

Another important concern is standardisation and good manufacturing practice. There are many manufacturers of the devices and their contents, largely based in China, and many different models, with limited quality controls in place. At the least, production must ensure that cartridges are filled true to label and that dose delivery is consistent. Without standardisation, the results from any particular study many not be generalisable because of uncontrolled variability in vapour content within or across studies.

Additionally, research is also impeded by a lack of regulation. To be approved as a medicine or medical device, specific requirements for manufacturing processes, design of the device, safety and efficacy must be met. However, to the best of our knowledge, no ENDS brand has yet been approved in any country as a medicine. Nevertheless, some regulation of safety standards is needed, possibly by licensing of the manufacturers in the country of manufacture, as FDA does for many pharmaceuticals exported from China to the US. Currently, there is no regulated requirement to manufacture at an approved site and to test every batch. In the absence of licensed manufacture and regulations, manufacturers may change product designs and contents at will, so that any research only applies to the specific ENDS model and batch tested with no certainty that the findings will apply to future models or batches.^{19 20} Furthermore, this technology evolves rapidly and research reports may become obsolete by the time they are published.

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Box 1 List of suggested studies

Non-clinical studies

- ▶ Composition of refill liquids.
- ▶ Composition of vapour.
- ▶ Product quality, description of the diversity of products and product change over time.

Animal studies

- ▶ Pharmacodynamics (PD), pharmacokinetics (PK), toxicokinetics.
- ▶ Toxicology, carcinogenicity.
- ▶ Effects of long-term exposure.

Clinical studies

- ▶ Deposition of droplets, exposure to nicotine, propylene glycol, flavours, etc.
- ▶ PD, PK, toxicity, carcinogenicity, infectivity.
- ▶ Addictive potential, abuse liability, risks of nicotine refill bottles.
- ▶ Puff topography, dosage, duration, reasons for use, brand switching.
- ▶ Optimal dosage, dosing regimen, effect of user experience with the device.
- ▶ Effect on tobacco withdrawal symptoms, adverse effects.
- ▶ Efficacy for smoking behaviour (cessation and reduction), comparison with nicotine replacement therapy (NRT).
- ▶ Efficacy for administering other medications.

Public health studies

- ▶ Prevalence of use in population subgroups.
- ▶ Utilisation patterns (long-term use), preferred brands, satisfaction of users.
- ▶ Use to administer illicit drugs or medications.
- ▶ Surveillance, pharmacovigilance, sales data.
- ▶ Effects of exhaled ('secondhand') vapour. Fewer fires and burns due to less smoking?
- ▶ Effect of good manufacturing practice on the quality of products.
- ▶ Economic studies, cost effectiveness, impact on healthcare costs.
- ▶ Impact on prevalences of quit attempts, quit rates and smoking in the population.
- ▶ Policy analysis, efficacy and impact of regulations, public opinion surveys.

Moreover, the puff strength had to be increased and the aerosol density decreased as the puff number increased, while smoking characteristics, such as vacuum and density, varied considerably within and between ENDS brands.⁵ The potentially adverse effects on lungs if strong suction is required to smoke ENDS needs to be documented in the long term.⁵

The fifth study found hazardous aldehydes in a Japanese brand of ENDS (formaldehyde: 8.3 mg/m³, acetaldehyde: 11 mg/m³ and acrolein: 9.3 mg/m³) in concentrations respectively 1.2, 137 and 30 times less than from the tobacco cigarette brands also tested.²² However, these concentrations largely exceed international maximum exposure limits for formaldehyde (2.5 mg/m³) and acrolein (0.8 mg/m³).^{29 30} Glycerol is used to improve mist generation, but if heated to 280°C can produce acrolein, a potentially critical toxicant in ENDS vapour, and other ENDS brands should be tested for it.

The sixth study tested the nicotine content in 2 brands of ENDS cartridges (3.2–4.1 mg/cartridge) and in the vapour of 1 brand (1 µg per puff for puffs 1–10, then <0.3 µg per puffs for puffs 11–50).¹⁴ This level was far below the levels found by FDA scientists,¹² and suggests malfunctioning of ENDS, as the authors found.

The seventh study found that ENDS advertised as containing E-Cialis did not contain tadalafil (ie, Cialis) but contained its analogue amino-tadalafil, and that ENDS advertised as containing E-Rimonabant contained rimonabant and an oxidative impurity of rimonabant.⁶ These products contained nicotine, even though they were advertised as containing no nicotine.⁶ The eighth study evaluated five brands of ENDS and found that fluid leaked out of most cartridges, that the labelling of cartridges was poor and that most packs lacked warning information about potential risks.²⁴

Thus, although some non-clinical research has been conducted that is relevant to predicting health effects in humans, much work remains to be done. For example, tests of pharmacokinetics and toxicokinetics should be conducted in animals (including absorption, distribution, metabolism and excretion of all compounds in ENDS vapour), and their toxicology and carcinogenicity should be characterised using standard tests of cytotoxicity and mutagenicity. Studies should also be conducted to explore the likely health effects of long-term ENDS

NON-CLINICAL STUDIES

The main objective of non-clinical studies is to determine the potential safety of ENDS in the short and long term by detecting potential target organs for toxicity, identifying safe dosage schemes and identifying parameters for clinical safety monitoring.

At the time of this writing, eight non-clinical studies had evaluated ENDS.^{5 6 14 20–24} A study carried out by the FDA on two brands of ENDS found that they contained carcinogens, namely tobacco specific nitrosamines (TSNA), albeit at lower levels than in tobacco cigarettes and in similar levels to those found in nicotine medications^{25 26}; that similarly labelled cartridges emitted markedly different amounts of nicotine with each puff (27–43 µg nicotine/100 ml puff); and that nicotine was detected in cartridges labelled as containing no nicotine.¹² Moreover, one cartridge contained 1% diethylene glycol, a toxicant implicated in mass poisonings.^{27 28}

The second non-clinical investigation, conducted by a private company funded by an ENDS manufacturer, showed that

the labelling of different ENDS approximately reflected their actual nicotine content.²⁰ TSNA and polycyclic aromatic hydrocarbons (potent, locally acting byproducts of the incomplete combustion of organic material) were detected in concentrations similar to those existing in nicotine medications.^{20 26} Unlike tobacco cigarettes, the ENDS tested did not appear to interfere with monoamine oxidase enzyme A and B activity; a process involved in the regulation of monoaminergic neurotransmitters that plays a pivotal role in mood and behaviour. Tests did not show detectable levels of heavy metals, propylene oxide and ethylene oxide, and found that ENDS probably incorporate lower concentrations of carcinogens than tobacco cigarettes.²⁰ These results accord with the findings of the third study of no measurable levels of polycyclic aromatic hydrocarbons in ENDS aerosols.²³

The fourth study compared the smoking properties of tobacco cigarettes and ENDS.⁵ Results showed that stronger puffing was required to smoke most ENDS brands than tobacco cigarettes.

use. The effect of good manufacturing practice in improving quality and minimising hazardous impurities needs to be assessed, and the effect of higher-voltage modified ENDS brands on hazardous volatiles should be monitored. Finally, there is a need to describe the variety of ENDS brands, models and refill liquids ('juice'), and their evolution over time.

CLINICAL STUDIES

Safety

Health risks are clearly important to evaluate, in particular, if the chemicals or any contaminants in ENDS cartridges or the vapours were toxic, carcinogenic or infective, or if the devices were used to deliver drugs of harm or drugs with addictive potential. As yet, there is no, or only very limited and conflicting data on toxicity, carcinogenicity and infectivity. Standardised methods for evaluating the safety of such novel potential reduced exposure products for tobacco users remain elusive,³¹ but safety studies are likely to involve topics such as pharmacokinetics (PK; drug concentration time course), pharmacodynamics (PD; drug action time course), deposition of vapour droplets, toxicity and abuse liability. In addition, ENDS cartridges are sometimes refilled with nicotine-containing liquid, and bottles of this liquid may be dangerous as they contain up to 1 g of nicotine: the fatal dose of nicotine is estimated to be 30–60 mg for adults and 10 mg for children.^{2–4} At the least, monitoring must be initiated to evaluate the public health effects of easy access to lethal nicotine doses that are sold in a pleasantly flavoured vehicle.

Pharmacokinetics, pharmacodynamics and effects on withdrawal

The efficacy of ENDS as a means of aiding smoking cessation is likely to depend largely on their ability to deliver nicotine to the brain at adequate doses and speeds, and PK and PD studies are important in this regard. To date, two reports, using different brands, have addressed the PK and PD of ENDS with respect to nicotine.^{7–8} In the first study, 32 ENDS-naïve smokers completed 2 bouts of 10 puffs from ENDS with an 18 mg or a 16 mg nicotine cartridge, or smoked a lit cigarette or puffed on an unlit cigarette.⁸ In contrast to tobacco cigarettes, the 16 mg and the 18 mg ENDS did not increase plasma nicotine or heart rate reliably. Importantly, ENDS reliably decreased tobacco withdrawal symptoms and increased

ratings of acceptability. These effects were sometimes greater than those observed during the unlit cigarette condition, but less than those observed during the lit cigarette condition.⁸

In the other report, a crossover trial of 40 ENDS-naïve participants, smokers were assigned on different days to use an ENDS with a 16 mg or a 0 mg nicotine cartridge, a nicotine inhaler, or their usual brand of cigarette.⁷ In a PK study involving a subgroup of nine participants, the 16 mg ENDS yielded a maximum nicotine concentration in blood plasma of 1.3 ng/ml, the inhaler 2.1 ng/ml and the tobacco cigarette 13.4 ng/ml. Importantly, the 16 mg ENDS, 0 mg ENDS and nicotine inhaler all significantly decreased desire to smoke. The tobacco cigarette produced the greatest decreases in desire to smoke. The 16 mg ENDS was rated as more pleasant than either the 0 mg ENDS or the inhaler.⁷

Another study of 11 smokers showed that ENDS decreased craving for tobacco after overnight smoking abstinence.⁹ Thus, there is some agreement between studies: the devices tested delivered far less nicotine than a tobacco cigarette, produced moderate suppression of craving and withdrawal, and were acceptable to users. The lower plasma nicotine after puffing from ENDS compared with smoking may be due to lower concentrations of nicotine in its vapour compared with tobacco smoke, and to lower absorption from the respiratory mucosa compared with alveoli.^{7–8} However, nicotine's PK/PD in ENDS users is almost certainly related to additional factors including puff number, volume and duration, nicotine dose, pH, vapourisation temperature and the user's experience with the device. These factors await parametric manipulation.

The extant PK/PD data regarding ENDS are generally confined to nicotine, although one study found that ENDS do not increase expired air CO, suggesting the carboxyhaemoglobin (COHb) concentration is unaffected.⁸ Other chemicals present in ENDS cartridges include medications, propylene glycol, flavours, additives and impurities.^{6,12} Propylene glycol is a solvent widely used in oral, intravenous and topical pharmaceutical products. The FDA has classified propylene glycol as an additive that is 'generally recognised as safe' for use in food.³² It is also commonly used in artificial smoke generators (eg, fire training exercises, theatre productions), and as an excipient in nasal sprays and nebulised solutions. It has low toxicity and lack of

carcinogenic effects, but when delivered intravenously in high doses may produce fatal lactic acidosis.³³ This observation suggests that PK/PD studies of ENDS should also include other potentially active chemicals to which users are exposed. Recent ENDS designs position the nicotine closer to the heating element. It is possible that different designs have improved nicotine delivery since the studies cited above were conducted. Similarly, better sealing of the nicotine cartridge may prevent nicotine degradation and leakage.²⁴

The extent to which ENDS vapour is inhaled into the lung, and where the particles are absorbed, is also uncertain.²⁰ Absorption may be a function of droplet size, as particles must be small enough to penetrate sufficiently for pulmonary absorption. This issue, relevant to product safety, nicotine dosing and abuse liability, requires study.

Abuse liability

The abuse liability of therapeutic nicotine products has long been a topic of concern and empirical investigation,^{34–36} and such studies should also be conducted for ENDS. Predicting abuse liability accurately is important: drugs/devices with high abuse liability represent a potential threat to public health and should be controlled with appropriate regulatory action (eg, restricting minor's access; requiring a prescription). Factors that contribute to abuse liability include reinforcing efficacy (will people work to obtain desired effects?), pharmacokinetics (how fast does the drug get to the brain?), dependence potential (does termination produce withdrawal, can use become compulsive?), adverse effects (does it make users sick?), and perhaps sensory characteristics.³⁴ ENDS vapour contains nicotine,^{14,21} and nicotine may be present in users' blood.⁷ The vapour may be delivered in a sweetened and flavoured vehicle (eg, fruit, mint and chocolate). There is, therefore, a need for clinical studies that use established methods to examine ENDS abuse liability as a function of device, medication, dose and flavour, in a variety of populations, including nicotine-naïve individuals, compared to relevant controls (eg, tobacco cigarettes and nicotine medications).

Efficacy

Pending product standardisation and demonstration of safety, clinical studies of tobacco dependence treatment efficacy are

needed. These studies may include intermediate outcomes such as reduction in cigarette intake, decreased tobacco withdrawal symptoms, improved respiratory symptoms and adverse effects.³⁷⁻³⁸ Laboratory work should examine which conditions lead to maximal effect (eg, are some doses more effective than others, is a particular instruction set or behavioural support required, how many cartridges should be used in a day?). Such preliminary studies are extremely valuable for establishing dosing regimens and predicting efficacy in subsequent treatment studies, while also addressing the product's safety profile. To date, three laboratory studies have found that ENDS decrease craving.⁷⁻⁹ Future studies might include parametric examination of the influence of cartridge dose, puff topography, and user experience on withdrawal symptoms and on smoking behaviour. Laboratory-based research should compare the influence of ENDS and approved nicotine medications.⁷

Several smoking cessation efficacy trials are already underway, in Italy, New Zealand and Canada.^{9, 39, 40} In their simplest form, efficacy studies might involve parallel-group designs in which cigarette smokers are randomised to receive behavioural treatment alone or behavioural treatment in combination with ENDS and 0 mg cartridges (placebo) or ENDS and nicotine-containing cartridges. Dose may depend upon smoking history, and more than one active dose arm may be of value. Other treatment trials will compare ENDS to approved smoking cessation products such as nicotine replacement therapy (NRT). In this regard, the nicotine inhaler is an obvious choice for comparison, given the similarity in the route of administration. However, the inhaler is less widely used than other cessation medications, and therefore optimal comparison products might be those that are most more widely used, acceptable and of proven effectiveness, such as nicotine patch, gum or tablet.⁴¹

The long-term use of medicinal nicotine as a harm-reduction strategy is increasingly being recognised as a possible therapeutic option for smokers who are unwilling or unable to quit.⁴²⁻⁴⁴ Smoking reduction may also facilitate cessation in these smokers.⁴⁵ However, ENDS will have a positive impact on the health of smokers only if they help people quit smoking, as partial reduction of cigarette intake may not be associated with a meaningful decrease in health risk.³⁸

The use of ENDS to administer other medications to the bronchi and lungs (eg, antibiotics, asthma medications) should also be explored.⁶ Finally, the effects of the long-term inhalation of the various ingredients in ENDS vapour should also be evaluated (nicotine, medications, flavours, humectants, etc.). As noted, there is some evidence that nicotine replacement is poor or non-existent with ENDS,^{7, 8} but product design evolves rapidly and future models may test differently. As urgent as this research may be, it must be conducted according to the ethical principles that govern all clinical research, in particular, ensuring that experimental procedures maximise potential benefits and minimise possible harms.

PUBLIC HEALTH STUDIES

Usage patterns and long-term exposure

ENDS are very popular. Google searches for 'electronic cigarettes' increased 5000% over the past 2 years,³ 9% of UK smokers have ever used ENDS and 3% were using them at the time of a recent survey.¹¹ Another survey found that 9% of Polish teenage smokers used ENDS.⁴⁶ However, few data exist on the characteristics of ENDS users, how and why they use ENDS in relation to tobacco products, smoking cessation medications and other drugs, and what users' perceptions and expectations are.^{1, 11, 18} The safety, toxicity and efficacy of ENDS will depend on how the product is used, and the balance of risks (tobacco vs ENDS) will only be beneficial if ENDS are mostly used for smoking cessation or relapse prevention, rather than for temporary abstinence, for smoking reduction or for dual use with tobacco cigarettes. Despite the limitations of self-report data, surveys provide data hitherto unavailable and would be useful to repeat on a regular basis to track time trends. Studies should also ascertain whether ENDS are used for the administration of illicit drugs or to inhale medications designed for oral use.⁶ Epidemiological studies should evaluate the impact of these products on quitting activity in the population, as it is possible that ENDS may elicit quit attempts in smokers who otherwise would not have attempted to quit. Finally, economic studies should assess the cost effectiveness of these devices (compared with approved smoking cessation drugs), and their impact of cigarette sales and on healthcare costs.

Surveillance

Because clinical trials that lead to regulatory approval of a drug or device will take

time and usually involve a very small fraction of the population who will actually use the product, or are conducted in non-representative samples, there is a need for post-marketing surveillance and pharmacovigilance. The ongoing collection of surveillance data can help establish the safety/toxicity profile of a product and contribute to its continued availability, modified labelling, or subsequent recall,⁴⁷ even though these efforts have been criticised for their voluntary nature, incomplete and inaccurate data, and other serious limitations.⁴⁸ However, in many countries, ENDS are available outside of a regulatory framework and are therefore not submitted to surveillance. Without valid and reliable ongoing surveillance, significant health effects may go undetected, putting lives at risk. To our knowledge, no serious adverse events have been reported to any national authority, but this is no guarantee that they have not occurred. Another need is for data on ENDS sales, which would enable tracking of sales in relation to tobacco control interventions such as tobacco price increases, and provide ecological evidence of the reasons for purchase.

Other considerations

A partnership with consumers is being seen by some as an essential part of good research practice.⁴⁹ However, researchers should be aware that, in North America in particular, ENDS consumer groups are well organised and active in advocating the right to use ENDS. These groups can provide useful input, but avoiding bias while collaborating with them might be challenging. Incidentally, these consumer groups themselves could be the object of research (eg, to assess their impact on legislation and public opinion).

There is potential for harm if ENDS vapours can be inhaled by others besides the user, in the same way as occurs with secondhand tobacco smoke. However, if ENDS were used as tobacco cigarette substitutes, the risk of smoking related fires and burns, a major public health problem,⁵⁰ would be reduced. Studies that examine the policy models for balancing such complex competing harms and benefits are required.

CONCLUSIONS

Many questions about ENDS remain unanswered. The priority is to characterise the safety profile of these products, including in long-term users. If these products were demonstrated to be safe, their efficacy for smoking cessation should

then be tested in appropriately designed clinical trials. A standard dosing regimen in these trials may be necessary for registration and practical purposes. A difficult question is how to implement such a research programme when these devices are developed and marketed by relatively small companies that may not have the resources and manpower necessary to comply with the regulation process, or even any interest in going through this process, especially because, in several countries, ENDS are marketed legally without going through clinical trials.^{16 17}

Therefore, there is an urgent need to develop resources and a legal framework to explore the safety and efficacy of ENDS. Ideally, these studies would have been conducted prior to marketing of these products. Until they are conducted, continued marketing constitutes an uncontrolled experiment and the primary outcome measure, poorly assessed, is user health. Whether ENDS should be prohibited until safety and efficacy data are published is currently debated.^{14 15 24} Tobacco takes a tremendous toll and smoking cessation substantially decreases smoking related deaths.⁵¹ Potentially, this research effort, contributing to the safety and efficacy of new smoking cessation devices and to the withdrawal of dangerous products, could save many lives.

Competing interests CB's salary is paid by The University of Auckland and his research is supported by grants from the New Zealand Health Research Council (HRC), the University of Auckland and the NZ Heart Foundation. He has previously undertaken tobacco control research supported by the New Zealand Ministry of Health, and by Nicovum, Sweden, prior to the purchase of this company by RJ Reynolds. He is currently an investigator on a study involving reduced nicotine cigarettes in which the products were purchased by the University of Auckland from Vector Group Ltd, US. He has previously undertaken research on ENDS funded by HealthNZ, in which the study products were supplied by Ruyan, Hong Kong; and he is the principal investigator on an HRC-funded efficacy trial of ENDS that will use products provided by a NZ-based ENDS retailer. Other than these relationships, he has no conflicts of interest to declare. TE's salary is paid by Virginia Commonwealth University and his research is supported by grants from the US National Institutes of Health (R01CA103827 and R01CA120142). In the past he has served as a paid consultant to the National Association of Attorneys General regarding litigation against a tobacco company. He has served as an expert consultant for the World Health Organization regarding ENDS. Also, he has been retained by the US FDA as a consultant but, as of this writing, has not served in this capacity in any way and has received no payment from the FDA. Other than these relationships, he has no conflicts of interest to declare. J-FE's salary is paid by the University of Geneva. He has served as an unpaid expert consultant for the World Health Organization regarding ENDS, and as a paid consultant for Pfizer, a manufacturer of smoking cessation medications, in 2006–2007 (on the Swiss varenicline advisory board).

The University of Geneva received trial medications from Pfizer in 2006 for a study conducted by J-FE. No competing interest since then. AF has no competing interests to declare. ML has researched various nicotine products including ENDS for several firms and universities, and advised several distributors, but has no financial interest in any of these.

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