



## E-Cigarette or Drug-Delivery Device? Regulating Novel Nicotine Products

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**O**n April 25, 2011, the Food and Drug Administration (FDA) announced its intention of regulating “electronic cigarettes” as tobacco products, having failed in its initial attempt to regulate them

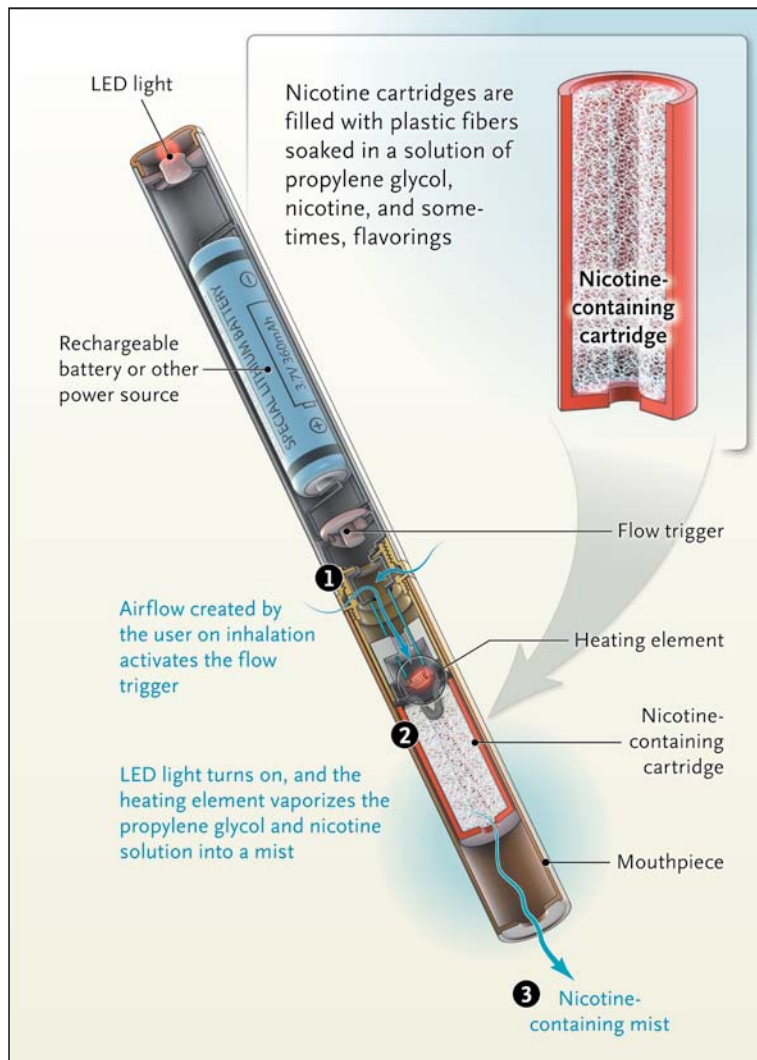
as drug-delivery devices. Previously, products delivering refined nicotine had either been regulated as pharmaceuticals (and subjected to the “safe and effective” standard used in drug approvals) or swiftly removed from the market to protect public safety. The FDA’s decision came after the courts blocked the agency from regulating these products as drug-delivery devices, holding that under the 2009 Family Smoking Prevention and Tobacco Control Act (FSPTCA), products containing nicotine derived from tobacco but making no therapeutic claims must be regulated as “tobacco products.”<sup>1</sup> Together, this ruling

and the FDA’s announcement have upended the status quo. Unless and until the FDA asserts its authority under the FSPTCA, manufacturers can sell concentrated nicotine products directly to consumers, raising serious safety concerns.

Nicotine, an alkaloid found in tobacco, acts as an agonist of nicotinic acetylcholine receptors in the peripheral and central nervous systems. A stimulant and the addictive drug in tobacco products, nicotine drives those products’ chronic use despite their well-known adverse health effects. Cigarettes typically contain 1 to 2 mg of nicotine, but nicotine has

substantial toxic effects at higher doses. The estimated lethal dose for a child is 10 mg, the content of about half a pack of cigarettes. Smoking tobacco leads to nicotine deposition in the alveoli, absorption into the arterial circulation, and delivery to the brain within seconds. Such instant gratification makes cigarettes the most addictive drug of abuse, with tobacco eclipsing cocaine and heroin in terms of users’ reported difficulty in abstaining.

The misleading term “e-cigarette” refers to an aerosolizing delivery device mated with a disposable cartridge. The cartridge contains nicotine in solution in a humectant, usually propylene glycol. The devices vary in construction, generally consisting of a battery, a heating element, a power source, and a pressure switch, all embedded in a tube with a mouth-



small bottle, allow consumers to fill used cartridges with replacement solution at higher doses than they originally contained. Propylene glycol is the most common humectant, and manufacturers claim that it's safe in consumer products. However, the safety of inhaling it, particularly over an extended period, has not been studied in humans.

Despite the FDA's statements, what is necessary or sufficient to constitute an e-cigarette — the delivery device, the cartridges, their contents, or a combination of the three — remains unclear. Historically, similar inhaler devices have used mechanical heat — the Eclipse cigarette, for example, heated tobacco soaked in glycerol — or have lacked a heat source, like the Favor inhaler of the late 1980s, which therefore released no visible aerosol. Favor reached the market briefly but was removed by the FDA. After the technology was sold to a pharmaceutical company, it eventually earned FDA approval as a safe and effective smoking-cessation aid (like the nicotine patch and gum) and was rereleased as the Nicotrol inhaler. But nothing limits the current generation of devices to delivering nicotine: instructions for filling cartridges with marijuana hash oil can be found on YouTube.

Exactly what variants of such nicotine-delivery devices will be allowed on the market, regulated or unregulated, and what doses of nicotine they will be permitted to deliver, is unclear. This uncertainty is worrisome, given that testing of cartridges has revealed poor quality control and marked inter- and intra-manufacturer variability in nicotine content, as well as large deviations from the

piece and a socket for cartridge insertion (see diagram). When the user draws on the mouthpiece, the negative pressure closes the switch, causing the heating element to warm both the cartridge and passing air. This warming causes the humectant to aerosolize, so that water vapor accumulates and forms a visible fog when exhaled. Nicotine, flavorings, and other additives or contaminants are carried with the aerosol into the oral cavity.

Despite being marketed as cigarettes, these devices have more

in common with pipes, multi-dose inhalers, nebulizers, or other devices loaded with a drug, whether regulated (such as albuterol) or illicit (such as cocaine). Currently, three related products are being sold: delivery devices, cartridges, and refill solutions. Cartridges generally contain up to 20 mg of nicotine and are device-specific; starter cartridges are bundled with each device sold but are primarily sold separately by the device manufacturer or other suppliers. Refill kits, including as much as a gram of nicotine in a

content claimed on the label.<sup>2</sup> Testing of the vapor from the devices has revealed similar variability, including marked “puff-to-puff” variation.<sup>3</sup> Finally, testing of users in laboratory settings revealed minimal blood nicotine concentrations.<sup>4</sup> Marketing claims aside, the devices tested did not efficiently deliver nicotine, much less deliver it into the arterial blood as tobacco smoke does. Smokers attempting to use e-cigarettes for smoking cessation will most likely find them ineffective; indeed, their use may instead perpetuate smokers’ addiction. Since evidence of both safety and cessation benefit is lacking, there is cause for concern that the devices will become “bridge products” for use in places where smoking is prohibited or as starter products that are attractive to young people or former smokers.

The ineffective nicotine delivery of today’s models cannot be seen as a permanent limitation. Increasing the cartridges’ nicotine concentration may increase deposition — marketers of refills advertise their escalating concentrations, and some sell bottles of solution containing enough nicotine to kill an adult if ingested. Manipulating the fluid by altering its acid–base status can increase bioavailability, since absorption in the mouth and proximal airways depends on the pH. Various temperature and flow characteristics may alter the particle size and absorption of the vapor. Finally, the lack of distal pulmonary delivery may not be an unsolvable problem<sup>5</sup>; modifications leading to arterial delivery could dramatically increase the risk of

addiction and abuse, as well as that of serious overdose. In fact, shortly after the FDA’s announcement, both Philip Morris and British American Tobacco purchased nicotine-inhaler technologies that promise pulmonary delivery — strategic decisions that are unlikely to be coincidental and almost surely presage future consumer products.

Ultimately, Congress, the courts, and the FDA must find an effective regulatory approach for nicotine products that minimizes risk and maximizes the public welfare. Refined nicotine delivered by inhaler devices should be included in any such regulatory scheme, as should tobacco products promising “reduced or modified risk.” To address the latter, the FSPTCA offers a new public health standard, requiring manufacturers and the FDA to focus on the goal of reducing the number of people who die or are harmed by tobacco, taking into consideration the risks and benefits to the entire population. For refined nicotine to ever be safely marketed under these standards, regulation must also include strict requirements — no different from those for other consumer drug products — for evidence of safety, consistent specifications, quality control, and functional dose limitations.

Regardless of how regulation of refined nicotine occurs, it must ensure that no existing or future products slip through the cracks. Some e-cigarette proponents have argued that strict regulation or withdrawal of the devices from the market would harm current users, forcing them to return to

smoking tobacco. In reality, both smokers and e-cigarette users have many alternatives: multiple nicotine products, approved, regulated, and deemed to be safe and effective by the FDA, are already widely available (in addition to other effective cessation tools, such as varenicline, bupropion, telephone quit-lines, and Web-based services). Pending more aggressive regulation, clinicians should advise patients wishing to use nicotine to stick to the FDA-regulated forms, such as patches, gum, lozenges, nasal spray — or even, perhaps, the existing FDA-approved inhaler.

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