

FDA Should Facilitate Investigational New Drug Applications (IND) for Commercially Available Electronic Nicotine Delivery Devices

Comment for Nicotine Steering Committee

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Policy issue

ENDS are widely available recreational nicotine delivery systems that are being promoted and used for smoking cessation. There are only limited data on the efficacy of ENDS when used specifically for smoking cessation and the existing trials are of low quality.¹ Some population-level studies find that daily users of high delivery ENDS do quit smoking (but not nondaily users of high delivery systems or users of cig-alikes).^{2 3} However, overall population-level studies show that ENDS are associated with a reduced likelihood of cessation as ENDS are used by most people.⁴

While these results are important for the FDA making decisions about the population-level impact of ENDS as actually used, they do not address the potential value of ENDS as a smoking cessation intervention as part of a clinically supervised quit attempt.

It may be possible that even though current use patterns do not support approval of widespread availability of ENDS as a recreational nicotine delivery device because of net public health harm, a more limited application of specific ENDS devices in a clinical setting could be beneficial.

¹ Hartmann-Boyce J, McRobbie H, Bullen C, Begh R, Stead LF, Hajek P. Electronic cigarettes for smoking cessation. *Cochrane Database of Systematic Reviews* 2016, Issue 9. Art. No.: CD010216. DOI: 10.1002/14651858.CD010216.pub3

² Hitchman SC, Brose LS, Brown J, Robson D, McNeill A. Associations Between E-Cigarette Type, Frequency of Use, and Quitting Smoking: Findings From a Longitudinal Online Panel Survey in Great Britain. *Nicotine Tob Res.* 2015 Oct;17(10):1187-94. doi: 10.1093/ntr/ntv078. Epub 2015 Apr 20.

³ Berry KM, Reynolds LM, Collins JM, Siegel MB, Fetterman JL, Hamburg NM, Bhatnagar A, Benjamin EJ, Stokes A. E-cigarette initiation and associated changes in smoking cessation and reduction: the Population Assessment of Tobacco and Health Study, 2013-2015. *Tob Control.* 2018 Mar 24. pii: tobaccocontrol-2017-054108. doi: 10.1136/tobaccocontrol-2017-054108. [Epub ahead of print]

⁴ Kalkhoran S, Glantz SA. E-cigarettes and smoking cessation in real-world and clinical settings: a systematic review and meta-analysis. *Lancet Respir Med.* 2016 Feb;4(2):116-28. doi: 10.1016/S2213-2600(15)00521-4. Epub 2016 Jan 14.

Unfortunately, conducting the relevant randomized controlled trials to assess the efficacy of any ENDS as a clinical smoking cessation device is, for all practical purposes, impossible. Manufacturers of ENDS have not to date conducted the required preclinical testing and academic investigators do not have the money.

Moreover, the existing FDA CEDR policies are designed to protect the public from exposure to potentially toxic substances that may have therapeutic value before these substances are widely available. Therefore, although ENDS are widely available to the public already, it is for all practical purposes impossible to conduct randomized controlled trials using ENDS.

FDA should make it possible for researchers to conduct clinical trials of commercially available electronic nicotine delivery devices for smoking cessation. This includes facilitating the investigational new drug (IND) process.

Rationale

There has been debate for many years about the potential benefits vs harms of ENDS in the general population. Some smokers are using ENDS to quit smoking with the potential of substantial health benefit. Others are using ENDS in combination with cigarettes (dual users), with little or no health benefit and the possibility of reduced quitting. A critical question is whether or not ENDS are effective for smoking cessation if used in a therapeutic context. There are a few small clinical trials with ENDS and smoking cessation, but not sufficient to answer the question of efficacy. Physicians and other health care providers have no information on which to counsel smokers who ask if they can use ENDS to try to quit smoking. At present it is nearly impossible for an investigator to obtain sufficient information about ENDS product safety to obtain an IND to study smoking cessation. Based on emissions testing, ENDS are believed by most experts to be less toxic than tobacco cigarettes. There needs to be a process to make it possible for investigators to obtain, with reasonable supporting evidence of safety, an IND to do the necessary clinical trials to address the question of potential benefit of ENDS.

Randomized controlled trials for smoking cessation could also provide important data on potential adverse health effects of ENDS.

Recommendations

Develop IND guidelines that are based on relative toxicity of ENDS compared to tobacco cigarette smoking, based on emissions testing. If ENDS emissions are judged to be substantially less toxic than cigarette smoke, grant INDs for controlled clinical trials. It is reasonable for FDA to require control groups consisting of currently approved smoking cessation medications, and study designs that would include assessment both of efficacy and safety.

Existing policy documents

None.