



September 8, 2010

Mr. Matt Salmon  
President  
Electronic Cigarette Association  
1401 K Street, N.W., Suite 600  
Washington, DC 20005

Dear Mr. Salmon:

FDA today has taken enforcement action against five distributors of electronic cigarettes and related components, for practices which violate various provisions of the Federal Food, Drug, and Cosmetic Act (FDCA). The warning letters issued today involve violations of good manufacturing practices, making unsubstantiated drug claims, and using the devices as delivery mechanisms for active pharmaceutical ingredients like rimonabant and tadalafil.

FDA intends to regulate electronic cigarettes and related products in a manner consistent with its mission of protecting the public health. FDA has determined that the electronic cigarette products addressed in the warning letters described above, and similar products, meet the definitions of both a drug and device under the Act and the definition of a combination product in 21 C.F.R. Part 3, with a drug primary mode of action.<sup>1</sup> Firms which introduce these products into the marketplace will have to comply with the FDCA, including the drug approval process as explained below. FDA invites electronic cigarette firms to work in cooperation with the agency toward the goal of assuring that electronic cigarettes sold in the United States are lawfully marketed.

The regulation of drugs in the United States (that are not part of FDA's Over-the-Counter Drug Review) is governed by the New Drug Application (NDA) process. The NDA is the vehicle through which drug sponsors formally propose that FDA approve a new pharmaceutical drug product for sale and marketing in the United States. Prior to filing an NDA, a firm submits to FDA an Investigational New Drug application (IND) in order to lawfully gather data on investigational products during animal studies and human clinical trials.<sup>2</sup>

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<sup>1</sup> See 21 USC 321(g), (h), and (p). For further general information on the regulation of combination products, please refer to the webpage for the Office of Combination Products at: <http://www.fda.gov/CombinationProducts/default.htm>. Although the agency has been granted separate authority to regulate tobacco products that are not drugs, devices, or combination products under the recently enacted Family Smoking Prevention and Tobacco Control Act, the e-cigarettes that FDA addressed in the warning letters, and similar products, meet the definitions in the Act for drugs and devices, with a drug primary mode of action.

<sup>2</sup> Please refer to 21 C.F.R. § 312 and the following link for detailed information about the IND application process: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/default.htm#preIND>

Upon submission of an NDA for electronic cigarettes and any other similar or related article, and the components thereof, the Center for Drug Evaluation and Research (CDER), one of the seven Centers within the FDA, will consult with other parts of the agency as needed, including the Center for Devices and Radiological Health (CDRH) as part of the application review process for these products.

Once the investigational phase is complete, the results may be submitted to FDA as a part of the NDA. In addition to the results of animal studies and human clinical trials, the NDA must also include proposed labeling, information about the active and inactive ingredients, clinical pharmacology, and the manufacturing and packaging process.<sup>3</sup>

Points of contact at CDER for specific information on the IND and NDA processes as they relate to electronic cigarettes and any other similar or related article, and the components thereof are as follows:

1. Sara Stradley or Parinda Jani of CDER's Division of Anesthesia, Analgesia, and Rheumatology Products at 301-796-2280 or
2. Melissa Furness of CDER's Division of Nonprescription Clinical Evaluation at 301-796-0893

A firm may schedule a pre-IND meeting to foster early communications in order for the Review Divisions to provide guidance on the data necessary to warrant IND submission.

In preparation for the meeting, we recommend that the company review any available literature and other accessible data on the products and provide to the Review Division a short summary of the studies and data that are available to support the safety and efficacy of the product for the proposed uses. At the pre-IND meeting, the Review Division can provide advice on the quality and amount of data that it would expect in the NDA.<sup>4,5</sup>

Regarding the amount and quality of data that would be necessary to obtain approval of a new drug, the agency issued guidance in 1998 concerning the amount and type of evidence needed to support effectiveness in an NDA. This guidance describes in some detail how we interpret the statutory requirements for adequate and well-controlled studies.<sup>6</sup>

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<sup>3</sup> Please refer to 21 C.F.R. § 314 and the following link for detailed information about the NDA process:  
<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/NewDrugApplicationNDA/default.htm>

<sup>4</sup> The following link provides information on good meeting management practices and principles:  
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079748.pdf>

<sup>5</sup> For further information about preparation for a productive Pre-IND meeting, please review the following link:  
<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/SmallBusinessAssistance/ucm069906.htm>

<sup>6</sup> The guidance, Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products, can be found at the following:  
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM078749.pdf>

FDA notes that an NDA would need to provide information including: a description of the chemistry of the drug substance and drug product, their manufacturing processes (which must comply with FDA requirements for Good Manufacturing Practices) and their controls (including in process and end product specifications); a description and characterization of the device; a characterization of the pharmacokinetic delivery of nicotine, including site of absorption and pharmacokinetic parameters associated with use at the recommended dosing level; non-clinical toxicology studies to support the safety of the proposed route of administration (note that the pulmonary route is considered a novel route of administration); any novel excipients and drug substance/drug product impurities; and data from adequate and well-controlled clinical trials to support the safety and efficacy of the product for the intended use.

If you propose your product for Over-the-Counter (OTC) use, you may need to perform consumer studies (label comprehension and actual use studies) in addition to the above mentioned efficacy studies in order to demonstrate that consumers can use these products without a learned intermediary.

Please consider sharing this information with your members.

Sincerely,

Janet Woodcock, M.D.  
Director  
Center for Drug Evaluation and Research