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SAFETY ASSESSMENT OF E-CIGARETTES IN US

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1. Introduction

In the US, electronic cigarettes (EC) fall in electronic nicotine delivery systems(ENDS) and usually contain nicotine derived from tobacco, flavorings, propylene glycol, vegetable glycerin, and other ingredients. These EC are electrically-driven devices consisting of the battery part and liquid, in an atomizer, which is aerosolized by applying energy and generating heat to a resistance encircling a wick. The substances mentioned above affect nicotine delivery, appeal, and ease of product use, influencing individual preferences that may play a role in use patterns. The popularity of EC is due to their ability to deal both with the physical (i.e., nicotine) and the behavioral component of smoking addiction. Sensory stimulation and simulation of smoking behavior and cigarette manipulation are important elements of a product's effectiveness in reducing or completely substituting conventional smoking/cigarettes, which are generally absent in nicotine replacement therapies and oral medications for nicotine dependence. This justifies why these products can be effective in lowering the consumption of tobacco smoking and are efficient as long-term replacements for a conventional cigarette or cigar [1]

2. Background and mechanism

Currently, there are three generations of EC in the US market [2].

First-generation devices: Regular cigarettes and consisting of small lithium batteries and cartridges (prefilled with a liquid that bathes the atomizer) with disposable or rechargeable batteries.

Second-generation devices: Higher-capacity lithium batteries and atomizers with the ability to refill them with liquid with atomizers with change in the head .

Third-generation devices (Mods): Large-capacity lithium batteries with integrated circuits that allow vapers to change the voltage or power (wattage) delivered to the atomizer. These devices can be combined with either second-generation atomizers or with rebuildable atomizers with consumers' ability to prepare their own setup of resistance and wick [2].

3. Safety & Risk assessment of EC in US

EC safety assessment can be evaluated in three steps in US:

3.1 Chemical Studies
3.2 Toxicological Studies
3.3 Clinical studies

3.1. Chemical Studies

Chemical studies evaluate the chemical composition of liquids and aerosols. These studies analyze environmental exposure (passive 'vaping'). Exposure to toxic chemicals from EC is far lower than tobacco cigarettes reported in several studies. Besides comparing the levels of specific chemicals released from tobacco and EC, it should be taken into consideration that the vast majority of the >4000 chemicals present in tobacco smoke are completely absent from EC [1].

3.2.Toxicological Studies

Toxicological evaluation of each of the ingredients of EC (e.g., nicotine, glycerol, propylene glycol, flavors, metals) and the mixture of the ingredients in the e-liquid and aerosol produced from the ENDS should be evaluated. Information concerning substances that may be solvent extractable from the container closure system or leachable into the e-liquid when the e-liquid is in contact with the container closure system should be evaluated [2]. Toxicological endpoints such as cytotoxicity, genotoxicity, carcinogenicity, and respiratory, cardiac, reproductive, and developmental toxicity need to be taken into consideration [2]

Based on the toxicological studies conducted so far, results have shown significantly lower adverse effects of EC vapor compared with cigarette smoke. However, no comparison with tobacco smoke was performed in any of these studies, and they cannot be considered relevant to EC use since the samples were not tested in the form consumed by vapors. More research is needed on EC, including studies on different cell lines, such as lung epithelial cells. In addition, evaluating a huge number of liquids with different flavors is probably necessary since a minority of them appear to raise some concerns when tested in the aerosol form produced by using an EC device [1].

3.3.Clinical studies

Clinical studies are very informative in evaluating *in vivo* effects on humans, which also helps monitor hundreds of users for many years to adequately explore the products' safety profile under investigation. Therefore, instead of conducting clinical studies that span months or years to evaluate potential clinical impact, information on possible long-term health impact by including existing longer duration studies in the public literature with the appropriate bridging information and extrapolating from short-term studies can be provided for clinical assessments [1].

4. Literature monitoring

Literature searches and monitoring are primarily intended to identify single case reports of adverse effects and to track any changes in benefit-risk profiles associated with the chemicals, particularly when new safety concerns arise. Literature monitoring includes published articles, articles, and reviews in indexed or non-indexed journals, any content posted anywhere online, posters and conference abstracts, etc .

Best Practices for literature monitoring techniques includes :
A drug safety expert with experience researching literature is needed.
Conduct risk assessments to ensure that the search criteria are robust and relevant to the objective of the literature search.
Conduct literature searches and evaluate the results for literature per regional requirements (Global and Local).

Literature search and review is therefore a critical activity that we in Clinchoice undertake for the safety profiling of drugs.

5. Conclusion

Based on the existing evidence, EC use is by far a less harmful alternative to smoking. There is no tobacco and no combustion involved in EC use; therefore, regular vapor may not contain several harmful toxic chemicals that are typically present in the smoke of tobacco cigarettes. Indeed, some toxic chemicals are released in the EC vapor as well, but their levels are substantially lower compared with tobacco smoke. EC are a revolutionary product in tobacco harm reduction. Although they emit vapor, which resembles smoke, there is literally no fire (combustion) and no 'fire' (suspicion or evidence that they may be the cause for disease in a similar way to tobacco cigarettes). Due to their unique characteristics, EC represent a historical opportunity to save millions of lives and significantly reduce the burden of smoking-related diseases worldwide [2].

6. References

[1] Konstantinos E. Farsalinos and Riccardo Polosa; Safety evaluation and risk assessment of electronic cigarettes as tobacco cigarette substitutes: a systematic review, Ther Adv Drug Safety, 2014, Vol. 5(2) 67–86.

[2] Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems, Guidance for Industry, 2019

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ClinChoice is a leading global Contract Research Organization (CRO), with over 4000 clinical research, regulatory, product vigilance, and toxicology professionals across North America, Asia, and Europe. For more than 28 years, ClinChoice has been providing high-quality contract research services to pharmaceutical, biotechnology, medical device, vaccine, and consumer healthcare product clients, encompassing a broad range of services and therapeutic areas.

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