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Division of Dockets Management (HFA-305)
Docket no FDA-2014-D-1939
Food and Drug Administration
5630 Fishers Lane, Room. 1061
Rockville, MD 20852

January 25, 2016

Nicopure Labs LLC ("Nicopure Labs") Comments on the Food and Drug Adminsitration ("FDA") Guidance - Use of Investigational Tobacco Products - Guidance for Industry and Investigators ("Guidance") (FDA-2014-D-1939)[1]

Nicopure Labs respectfully submits comments to the above captioned docket. Mindful of the fact that the docket comment period has closed, we nevertheless appreciate FDA's receptiveness to industry input at any time and thank FDA for this opportunity to share our views.

I. Introduction

Since 2009, Nicopure Labs manufactures and distributes both nicotine-containing and non-nicotine liquids (e-liquids) for use with vaping devices, as well as hardware recommended for use with its e-liquids. Nicopure Labs' leading e-liquid brands Halo and eVo are sold in the U.S. and in over 65 other countries. The company also distributes proprietary Reactor, Tracer, Triton and G6 vaping devices, which are recommended for use with the company's e-liquids. Nicopure Labs products comply with applicable REACH regulation in the European Union (EU), as well as with all EU labeling requirements, which include nicotine warning pictograms and specific ingredient and country of origin disclosures. The e-liquids are currently manufactured in Nicopure Labs' 100,000 sqf facility in Gainesville, Florida, with utmost care for the integrity of the manufacturing process and quality controls. The products are sold in bottles equipped voluntarily with child resistant, tamper evident caps. The nicotine content ranges from 0 mg/ml to 24 mg/ml. The e-liquids are manufactured from USP grade propylene glycol, glycerin and nicotine, they are diacetyl-free and they are made with flavorings sourced from reliable suppliers who also supply flavorings to other FDA regulated industries. Careful consideration is given to product stewardship. Test results of Nicopure Labs e-liquids with respect to absence of diacetyl and acetyl propionyl are available at https://www.halocigs.com/blog/halos-eliquid-test-results/. Furthermore, Nicopure Labs provides Safety Data Sheets for its products to its distributors and retailers.

These comments will discuss the Guidance applicability to vaping products at a future date.

[1] 80 Fed. Reg. 57623 (Sept. 24, 2015)

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II. Statutory and Other Relevant FDA Background

Section 910(g) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C 387j(g)) gives FDA the authority to issue regulations to exempt tobacco products intended for investigational use from the requirements of Chapter IX of the FD&C Act, including premarket submission requirements. To date, FDA has not issued such regulations, and consequently investigational tobacco products ("ITP") are not exempt from FD&C Act requirements, including premarket submission requirements.

As FDA correctly pointed out in the Guidance preamble, FDA's guidance documents, including this Guidance, do not establish legally enforceable responsibilities. Nevertheless, the Guidance implies that FDA and other federal agencies might not approve of, fund, or evaluate, results of research conducted in disregard of this Guidance, and therefore the Guidance has, in fact, binding effect on researchers and sponsors. This is conclusion is similar to some of the concerns raised in the joint Society for Research on Nicotine and Tobacco ("SRNT") et al. submission to the docket.

At present, vaping products are not under FDA oversight as tobacco products, although it is our understanding that imminently FDA will issue regulation attempting to bring vaping and other nicotine or tobacco-containing products under the statutory framework of the 2009 Family Smoking Prevention and Tobacco Control Act ("FSPTCA"), which amended the FD&C Act.

Also, it has come to our attention that the National Institutes of Health ("NIH") have issued a guidance to researchers in the form of Frequently Asked Questions ("FAQ"), with clear input from FDA's Center for Drug Evaluation and Research ("CDER"), to assist investigators that seek funding from the National Institute on Drug Abuse ("NIDA") and other NIH institutes for studies evaluating electronic cigarettes and other vaping products. [2] The NIH FAQ document suggests that an Investigational New Drug application ("IND") is required if the electronic cigarettes are intended for use in a clinical investigation for a therapeutic purpose (e.g., smoking cessation), although the same document confusingly concedes that "the requirement for an IND depends on the intended use" - presumably of the product as marketed at present or in the future, and therefore research on vaping products currently on the market should never be required an IND. To our knowledge, no vaping products are currently marketed in the U.S. with a drug claim or an intended use for smoking cessation. Furthermore, consistent with *Sottera,*[3] FDA may not regulate electronic cigarettes as drugs absent a drug claim.

Because at present vaping products are not under FDA jurisdiction, it would appear that vaping products could be used in human research, including that involving a "clinical endpoint", without substantial impediments. However, the reality is quite different.

[2] http://www.drugabuse.gov/researchers/research-resources/faqs-clinical-studies-involving-electronic-cigarettes-inds

3 Sottera Inc. v. U.S. Food and Drug Administration, 627 F.3d 891 (D.C. Cir. 2011)

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We were approached by independent researchers[4] who would like to use our product in studies involving human subjects. During the ensuing discussions it has become clear to us that the current FDA IND guidances, FAQs and general FDA approach to e-cigarette research resulted in unsurmountable obstacles to meeting the submission requirements for virtually all behavioral e-cigarette research, and certainly any research involving human subjects conducted by independent researchers. Additional obstacles to research are now raised by the Guidance. This situation is particularly troublesome as FDA has repeatedly emphasized that more science is needed to support regulation of vaping products, that FDA is a science-based institution and that FDA can only regulate as far as the regulatory science takes it. Thus, it is inconsistent with FDA's public health mission that the vaping products FDA is about to regulate, and which hold a tobacco harm reduction promise, may not be researched in the U.S. because of FDA-imposed practical impediments that will be detailed below.

We therefore respectfully urge FDA to **withdraw** this guidance and instead engage in notice-and-comment **rulemaking** under Section 910(g). We also respectfully ask FDA to ensure coordination between the Center for Tobacco Products ("CTP") and CDER to ensure that investigations on vaping products not intended to be sold to consumers with a drug claim may be freely conducted without an IND, as these products will fall, at best, under exempted tobacco products, when FDA's deeming rule is issued, but in any event these products are not under CDER's jurisdiction – unless a drug manufacturer explicitly commissions research clearly intended to support a New Drug Application. We believe, as do investigators who have approached us for use of our products in their research, that safety and ethical concerns can be addressed by the same institutional mechanisms that currently, and for decades, have ensured safe and ethical conduct of research involving commercially marketed tobacco products in a broad range of studies, including the use of various products to achieve smoking cessation, smoking reductions and relief of withdrawal symptoms. Ironically, many of those studies involve products, such as cigarettes, that are far more hazardous than electronic products.

III. The Guidance Raises Unsurmountable Barriers to Research

The Guidance proposes to bring "nonclinical laboratory studies" under FDA oversight. These are defined as "in vivo or in vitro experiments . . . in test systems under laboratory conditions". Also, the guidance suggests that all vaping products currently on the market, if used in clinical investigations, would require an ITP application. Other than the problematic assertion of jurisdiction, which was addressed in comments by other industry members[5], the Guidance's application results in massive document production requirements from manufacturers who are in fact not even sponsors of most of the current research, and will most certainly prevent independent researchers from ever conducting investigations on vaping products.

[4] For convenience, we will refer to research or academic institutions that are not contracted or sponsored for a specific study on vaping products by vaping, pharmaceutical or tobacco industry to conduct research as "independent researchers".
[5] See the submissions to FDA-2014-D-1939 docket by R.J.Reynolds Tobacco Company and Ballantyne Brands LLC.

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Here are some of the types of information the Guidance requires, among other, and that independent researchers, with no affiliation and no leverage over manufacturers, must provide in support of their investigations:

- A description of the investigational tobacco product and any comparator or placebo to be used in the study (this information may be provided in a table format), including each product's composition, design, and manufacture, that includes:
  o A description of the product design with schematics of the complete product and product components, a description of the design features (e.g., location of ventilation holes, heat source, paper porosity, coatings, nicotine concentration gradient), and performance specifications;
  o A complete list of, or a reference to the manufacturer's complete list of, uniquely identified components, ingredients, and additives by quantity in the tobacco product, including product chemistry and a table of any harmful or potentially harmful constituents (HPHCs), as well as the applicable specifications and a description of the intended function of each;
  o The name and address of the manufacturer of the tobacco product;
  o A description of the methods, facilities, and controls used for the manufacture, processing, packing, and storage of the tobacco product; and
  o Data and information sufficient to demonstrate the tobacco product will be stable during the conduct of the study.

We note that the University of California at San Francisco commented on this very issue as follows:

"If academic and public health researchers wish to conduct research on ITPs that (by definition) are not *legally* marketed, but are available in the marketplace to consumers and researchers alike, these researchers would not have access to the detailed and possibly proprietary information (including descriptions of design features, performance specifications, product chemistry, methods of manufacture, and other product information requested on pages 8-9 of the proposed guidance) required by FDA. In such cases, the researchers should be permitted to use these products for investigational purposes, and FDA should waive the requirement to submit information to which these researchers could not possibly have or legally gain access. FDA apparently recognizes this problem, and appropriately states on page 8 of its proposed guidance that researchers may, where applicable, submit "an explanation of why such information is unavailable"."[6]

It is virtually certain that manufacturers who do not sponsor a particular investigation would be unwilling to share proprietary, confidential and competitively sensitive information, such as the information listed in the Guidance, with anyone, including independent researchers. Therefore, rulemaking, rather than a guidance, is the proper avenue to address ITP requirements, and in any event detailed product- and manufacturing-specific information should never be required of independent researchers because it is generally not obtainable. Furthermore, even if confidential information could be protected by direct submission through the FDA Drug Master File, manufacturers may still be reluctant to deploy resources in support of studies

[6] *See "*UCSF comment on FDA draft guidance on investigational use of tobacco products" at https://www.tobacco.ucsf.edu/ucsf-comment-fda-draft-guidance-investigational-use-tobacco-products

they have not commissioned. Finally, the detailed product information required in the Guidance is likely only available to only a few large manufacturers and probably not to smaller manufacturers or importers, who represent the vast majority of the industry, and whose products are used by millions of Americans.

IV. The Guidance Does Not Address Current NIDA FAQ

Since about 2014 researchers wishing to engage in any vaping product investigation involving human subjects that potentially results in the subjects' partial or total substitution of cigarette smoking with the use of the researched vaping products, if funded by NIH or FDA, have been asked to file an IND for the respective vaping product. This requirement is imposed irrespective of the intended future commercial use of the product, and irrespective of its legal status (whether currently unregulated, or a tobacco product).

To our knowledge, to date no researcher has been able to collect the necessary information to file an IND for a vaping product, nor has any manufacturer volunteered to assist with a Drug Master File. The situation was brought to FDA's attention in early 2015 by several reputable organizations, with no satisfactory solution to this date.[7]

Conceptually, any manufacturer of a currently unregulated vaping product will oppose referring to the respective vaping product as "drug" even if only on an IND form, since the respective manufacturers do not see themselves as drug manufacturers and the product does not meet the drug definition, which reads:

"(A) articles recognized in the official United States Pharmacopoeia, official Homoeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them; and (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (D) articles intended for use as a component of any articles specified in clause (A), (B), or (C)".

Thus, between ITP requirements and IND requirements, future research on vaping products seem to be facing the ultimate Catch-22 situation, to the detriment of public health and scientific progress in general.

Furthermore, should the Guidance be applied as is, even in-house vaping product development would come to an abrupt stop once vaping products are regulated. This certainly cannot be FDA's intent, given that FDA has repeatedly stated that vaping products have a clear tobacco harm reduction potential and, in our company's view, these products' harm reduction potential can only be maximized through innovation and research.

The Guidance is entirely silent as to what requirement (IND or ITP) is applicable to dual, cigarette and non-combustible, product use research on any two or more tobacco and non-tobacco products (as very few

[7] SRNT, AACR et al letter to Commissioner Hamburg dated February 16, 2014 Regarding Requirement of Investigational New Drug Application for Clinical Studies Involving Electronic Nicotine Delivery Systems ("ENDS" or "Electronic Cigarettes")

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currently regulated tobacco products to date have received a marketing order, and the vast majority of currently regulated products are provisionally on the market and still under FDA review). This will create unnecessary confusion and jurisdictional overlap among centers within FDA. The FSPTCA clearly contemplates clinical investigations of new tobacco products that may address the impact of such products on smoking behavior that may include a smoking cessation outcome. The statute provides that FDA's new tobacco product premarket review must include an assessment of smoking behavior, including the "increased or decreased likelihood that existing users of tobacco products will stop using such products," and further provides that the determination "shall, when appropriate, be determined on the basis of well-controlled investigations, which may include 1 or more clinical investigations . . .". Therefore, any future FDA regulation of ITPs will have to clearly exempt tobacco products from IND requirements in the context of new product development and research.

V. Conclusion

To sum our submission, FDA should withdraw the Guidance and follow the required rulemaking pathway under Section 910(g) of the FD&C Act to address ITPs. FDA should also instruct CDER staff to refer all tobacco product matters to CTP, including research on vaping products, which will presumably be brought under FDA jurisdiction at a future date.

As always, we remain at FDA's disposal to answer any related questions.

With kind regards,

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