February 16, 2015

The Honorable Margaret Hamburg
Commissioner
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

Regarding: Requirement of Investigational New Drug Application for clinical studies involving electronic nicotine delivery systems ("ENDS" or "Electronic Cigarettes")

Dear Commissioner Hamburg:

Tobacco use remains the leading and preventable cause of death and disease in the United States. In fact, on current course, the rate of nearly one half million premature deaths per year will show little abatement unless more is done to reduce combustible tobacco product use. This was laid out starkly in the 2014 Surgeon General Report (Chapters 15 & 16 in particular) which trumpeted tobacco control successes, but also acknowledged the limitations of extant prevention and cessation efforts. That report acknowledges the potential importance of noncombustible tobacco products such as electronic nicotine delivery systems (ENDS) in turning the tide on the epidemic. It makes clear the power and mandate of the FDA's new authority over tobacco products to *"employ science-based rulemaking to reduce the impact of tobacco products at the population level, … to regulate existing and new tobacco products and to educate the public in order to reduce the death, disease, and other costs associated with use of tobacco products."(*page 859).

The FDA regulates products on the basis of a science foundation, and the FDA has done much to foster essential regulatory research including vital ENDS research. This included collaborating with NIH on the November 2013 conference on electronic cigarette research. All agreed that research is urgently needed to guide regulation, public health messaging, and policy. Furthermore, it was apparent then and even more so now that there is great diversity and rapid evolution in ENDS products that require study. The market size and rates of ENDS use in the population from youth to adult have also increased dramatically. Many of the most vital public health issues concern the behavior of users, patterns of use, factors that sustain use, reasons for use, consequences of use and impact on cigarette smoking and other tobacco use. The research community has responded quickly with grant applications for new research, and proposals to extend ongoing research to incorporate ENDS. Most unfortunately, these researchers have learned that many of the highest research priority studies may not be possible in the near term, if at all.

We are writing to you because some of the most urgently needed research to guide regulation and tobacco control policy is being shelved and the efforts of our nation's leading investigators and laboratories stymied by a regulatory action that is preventing vital ENDS research from being done. That regulatory action is the determination by CDER that Investigational New Drug Applications (INDs) are required very broadly for clinical studies involving ENDS (e.g., studies assessing effects on craving, withdrawal, smoking cessation, and other phenomena of vital scientific, clinical and regulatory importance ). This regulatory hurdle makes clinical research with most if not all commercially available products impossible because scientists do not have access to the required information that would allow them to

obtain IND applications. Most of the products are manufactured in China, and the detailed information necessary to complete the Drug Master File (DMF) section of the IND application is not available. Furthermore, the second and third generation products already on the market are designed to rely upon various commercially available fluid solutions ("juice") made by broad range of manufacturers, large and small, many of which are based outside the US and with no practical way for investigators to obtain DMF information.

Most of what we know about the clinical effects of tobacco products is from research conducted without the requirement of an IND, and includes effects on craving, withdrawal, patterns of use, and cessation – spontaneous or due to manipulation of tobacco products. These included studies of a wide range of cigarette brands, types of cigarettes, including denicotinized cigarettes, smokeless tobacco products, lozenge-type products such as Arriva, dissolving strips and more. Study safety and ethical issues were addressed by working to ensure that people were not exposed to higher levels of nicotine and other substances than they were already likely exposed to using licit and commercially available products. As is the case with ENDS, those studies were conducted with products that were neither designed nor manufactured so as to meet the standards of approved or potentially approvable drug products along with the information needed for DMFs.

Researchers have found that US ENDS marketing companies that have been approached do not have or are unwilling to share information required for the DMF, several claiming that they do not even have access to such information. To be clear, we are not discussing IND requirements that might be appropriate for sponsors of products seeking FDA approval of a specific ENDS product for therapeutic use, such as for approval and labeling as smoking cessation product via a New Drug Application. In such cases we would defer to negotiations between the FDA and the sponsor as to what information would be needed and if that would include an IND requirement as is typical in new drug product development.

An informal survey of investigators by way of the SRNT membership email list revealed that several investigators have already learned that they will not be able to conduct studies that had been approved by NIH review committees and in some cases funded by the NIH or FDA. Other investigators are simply ceasing work on grant applications until a workable path is developed. Some of this is work that was inspired by the November 2013 NIH FDA ENDS research conference and has the potential to address what were determined to be high priority needs of FDA itself.

We do appreciate the efforts of NIH staff to begin to work on contracts for research grade investigational ENDS products and associated Master Files for INDs but this may take several years, during which the commercially-marketed products which are evolving month by month will not be investigated – at least not in the United States. Furthermore, many of the technical designs of products of great scientific and clinical interest are evolving and will not likely be produced through NIH contracts.

We urge you to consider that for decades, and continuing today, a broad range of tobacco products have been and are being investigated in laboratories without INDs just as a broad range of commercially available drug products are investigated without INDs. The ethical and safety issues are addressed by reasonable assurance that the products used are within the range of what the research volunteers are already using and that the amount and duration of use will not be so high or without constraint as to put them at greater risk than can and does occur with the use of commercially available products. These research studies have been invaluable in assessing the theoretical viability of various tobacco products to reduce withdrawal and/or cigarette smoking, promote cessation, and inform public policy and education. Such research does not supplant the considerable additional research that may be required by FDA for approval of NDAs, drug indications, and claims. Although the focus of this letter is research pertaining to ENDS, we are aware that within the last two years the IND issue has been raised with respect to a commercial cigarette product (Quest®) and to a study involving smokeless tobacco products.

In short, the inability to conduct research on ENDS or any other current and future tobacco products because of the requirement to obtain INDs, which appear practically impossible to obtain, threatens public health because we do not understand and cannot study the impact of products being used by millions of people in the US. While research without an IND can be conducted to assess certain risks

associated with ENDS constituents, assessing their potential benefit to help quit smoking and many other clinically related effects cannot be conducted, thus preventing the scientific community from assessing whether any positive benefit result from the use of ENDS products. This information is vital to their appropriate and health-protecting regulation.

We would be pleased to meet with you and your staff to provide additional perspectives, and develop a workable path to make possible and expedite research on ENDS, including the identification of more viable and more appropriate mechanisms of oversight than the IND application process.

Sincerely,

Thomas Gould, PhD
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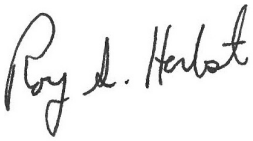

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