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June 21, 2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration
Docket No. FDA–2014–N–0189

RE: More evidence against "continuum of risk" related to heart disease

The paper, "Discontinuation of Smokeless Tobacco and Mortality Risk After Myocardial Infarction," by Gabriel Arefalk, MD; Kristina Hambraeus, MD; Lars Lind, MD, PhD; Karl Michaëlsson, MD, PhD; Bertil Lindahl, MD, PhD; Johan Sundström, MD, PhD, published on On June 24, 2014, by *Circulation* (DOI: 10.1161/CIRCULATIONAHA.113.007252) speaks directly to the assumed "continuum of risk" that the FDA is assuming exists.

This paper examined the drop in mortality following acute myocardial infarction among people in Sweden who quit smoking or quit using snus (a form of smokeless tobacco that is widely promoted as less dangerous than smoking cigarettes) compared to people who continued their tobacco use. They found that both quitting smoking and quitting snus had essentially the same effect on reducing mortality risk following an acute myocardial infarction (and adjusted hazard ratio of 0.54, 95% CI 0.32-1.02 for stopping smoking and 0.51; 95% CI .29-.91 for stopping snus) despite the fact that the snus users do not inhale combustion products.

The authors attributed this to the effects of nicotine on the autonomic nervous system, risk of arrhythmias, and effects on endothelial function, all of which affect risk of subsequent cardiac events, including death.

Note that none of these effects are reflected directly in hemodynamic changes, but rather deal with other pathways by which exposure to nicotine and tobacco products increases the risk of cardiovascular events. This is an important fact to keep in mind when considering the results in the another paper polished the same day, "Acute effects of using an electronic nicotine-delivery device (electronic cigarette) on myocardial function: comparison with the effects of regular cigarettes" by Farsalinos KE, et al. (*BMC Cardiovascular Disorders* 2014, 14:78 doi:10.1186/1471-2261-14-78) which found that e-cigarette use has smaller hemodynamic effects than smoking a cigarette. Assuming that this result is confirmed in additional studies, it does not absolve e-cigarette exposure or nicotine from the likelihood of producing adverse cardiovascular effects.[*]

[*]These issues are addressed in two earlier public comments submitted to this docket: Stanton Glantz PhD, FDA should not make regulatory decisions based on the "continuum of risk" theory until it has affirmative evidence that, as actually used, e-cigarettes or other tobacco products lower population risk. Comment tracking number 1jy-8coc-4qht; Suzaynn F. Schick, PhD, Ganna Kostygina, PhD and Carolyn Calfee, MD, The "Continuum of Risk" Must Include Cardiovascular Disease. June 6, 2014. Comment tracking number 1jy-8clb-hgy6.

There are three important implications of the snus study published in *Circulation* for the FDA's rule making:

- It is further indication that assumptions that other nicotine delivery systems that deliver nicotine without combustion products (whether snus, other forms of smokeless, or e-cigarettes) are, at least for some end points, no less dangerous than conventional combusted cigarettes.
- It is one more short term benefit of ending smoking and nicotine exposure that needs to be considered in the Regulatory Impact Analysis.
- It demonstrates that the Regulatory Impact Analysis, which presently only considers the effects of smoking and smoking cessation on disease incidence, needs to consider the effects of exposure to tobacco products on the progression of disease among people who are already sick. By ignoring these effects, FDA substantially underestimates the benefits of regulations that lower use of tobacco products.

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