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**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**

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Docket No. FDA-2014-N-0189

At several places in the proposed rule (pp. 23143, 23147-23148, 23152, 23176) the FDA states that it plans to consider the "continuum of risk" when making regulatory decisions about e-cigarettes. In particular, CTP Director Mitchell Zeller has, on several occasions, repeated the view that "It's not the nicotine that kills half of all long-term smokers, it's the delivery mechanism. ... We have to recognize some of these realities and figure out how they can impact regulatory policy."¹ The FDA proposes placing different warnings on different categories of products, which could apply to e-cigarettes, different classes of cigars and (although they are not addressed in this proposed rule) smokeless products. FDA emphasizes "the carcinogens in smoke and dangers of secondhand smoke," so all other "non-combustible" products could also get relatively favorable regulatory treatment under this proposal (see pp. 23144 and 23147).

While it is true that "it is not the nicotine that kills half of all long term smokers," it is also true that nicotine, by itself has important adverse health effects beyond the fact that it is the addictive drug that keeps people using tobacco. In addition, cancer is not the only, or even the largest cause of death due to smoking. In 1965-2014 cardiovascular and metabolic disease killed 8.8 million people (7.8 million smokers and 2.2 passive smokers) compared to 6.9 million from cancer (6.6 million smokers and .3 million passive smokers).² The dose-response curves – and indeed the direct effects of nicotine – in these disease processes are very different, with the cardiovascular system exhibiting a nonlinear dose-response relationship with large effects at relatively low doses.

In terms of the products addressed in the proposed rule, the one that is most likely to be the beneficiary of "continuum of risk" theory is e-cigarettes because they deliver nicotine in an aerosol that is not made by burning tobacco and so the aerosol contains fewer carcinogens. For this reason this comment concentrates on e-cigarettes.

¹ Clarke T. FDA aims to develop e-cigarette standards; nicotine policy. Reuters. June 11, 2014.
<http://www.trust.org/item/20140611224252-ieqd0>

² US Surgeon General. The Health Consequences of Smoking – 50 Years of Progress. Executive Summary Table 1.

There are, however, several factors that may prevent such a theory from being realized.

- E-cigarettes deliver levels of ultrafine particles that are smaller and often higher in number than conventional cigarettes.³
- In terms of at least one important outcome, the level of exhaled nitric oxide, nicotine-containing e-cigarettes, nicotine-free e-cigarettes, and conventional cigarettes had almost the same effects. For this outcome there is no difference in risk.⁴
- The effects of fine particles on cardiovascular risk accrue at very low levels of exposure and increase rapidly.⁵
- There are high levels of dual use of e-cigarettes with cigarettes.⁶
- There is rapid and accelerating penetration of the youth market, including substantial numbers of youth who initiate nicotine addiction with e-cigarettes.⁷
- While there is some evidence that e-cigarettes have been useful for helping motivated smokers who are using them to quit smoking cigarettes,⁸ the broader effect in the population of all smokers is that e-cigarette use is associated with lower -- not higher -- probability of quitting.⁹
- The FDA is not proposing any restrictions on advertising of e-cigarettes despite the fact cigarette advertising causes youth to smoke¹⁰ and e-cigarette advertising looks just like cigarette advertising.¹¹
- The e-cigarette companies are now almost entirely owned by cigarette companies whose profit maximizing goals will lead them to manage the e-cigarette market in a way to maintain cigarette smoking (which is more profitable than e-cigarettes) for as long a possible.
- There is an established process for e-cigarette companies to obtain FDA approval for making such claims and, as of June 13, 2014, not a single company has submitted the evidence to support such a claim.

All these factors combine to indicate that, while a puff on an e-cigarette may be less toxic than a puff on a cigarette, the overall effect on population health, which the FDA is required to consider, will be negative.

³ Grana RL, Benowitz N, Glantz SA. E-cigarettes: a scientific review. *Circulation* 2014 May 13;129(19):1972-86. doi: 10.1161/CIRCULATIONAHA.114.007667. Marini S, et al. *Toxicology and Applied Pharmacology* 2014; 278:9-15.

⁴ Marini S, et al. Short-term effects of electronic and tobacco cigarettes on exhaled nitric oxide *Toxicology and Applied Pharmacology* 2014; 278:9-15.

⁵ Institute of Medicine. *Secondhand Smoke Exposure and Cardiovascular Effects: Making Sense of the Evidence*. 2009. Also see Barnoya J, Glantz S. Cardiovascular effects of secondhand smoke: nearly as large as smoking. *Circulation* 2005 May 24;111(20):2684-98 and Grana RL, Benowitz N, Glantz SA. E-cigarettes: a scientific review. *Circulation* 2014 May 13;129(19):1972-86. doi: 10.1161/CIRCULATIONAHA.114.007667.

⁶ Grana RL, Benowitz N, Glantz SA. E-cigarettes: a scientific review. *Circulation* 2014 May 13;129(19):1972-86. doi: 10.1161/CIRCULATIONAHA.114.007667.

⁷ Centers for Disease Control and Prevention. Tobacco product use among middle and high school students--United States, 2011 and 2012. *MMWR Morb Mortal Wkly Rep*. 2013 Nov 15;62(45):893-7. Erratum in: *MMWR Morb Mortal Wkly Rep*. 2013 Nov 22;62(46):940. Dutra LM, Glantz SA. Electronic Cigarettes and Conventional Cigarette Use Among US Adolescents: A Cross-sectional Study. *JAMA Pediatr*. 2014 Mar 6. doi: 10.1001/jamapediatrics.2013.5488. [Epub ahead of print]

⁸ Brown J, Beard E, Kotz D, Michie S, West R. Real-world effectiveness of e-cigarettes when used to aid smoking cessation: a cross-sectional population study. *Addiction*. 2014 May 20. doi: 10.1111/add.12623. [Epub ahead of print]

⁹ Grana RL, Benowitz N, Glantz SA. E-cigarettes: a scientific review. *Circulation* 2014 May 13;129(19):1972-86. doi: 10.1161/CIRCULATIONAHA.114.007667.

¹⁰ US Surgeon General. *Preventing Tobacco Use Among Youth and Young Adults*. 2012. Chapter 5: The Tobacco Industry's Influences on the Use of Tobacco Among Youth.

¹¹ http://tobacco.stanford.edu/tobacco_main/ecigs.php Accessed June 14, 2014

Such a result is not without precedent: Even on the assumption that dose-per-dose of nicotine smokeless tobacco exposes users to lower risks, promotion of smokeless tobacco as a "harm reduction" strategy would have no net population benefit because of changes in initiation and cessation and dual use.¹²

The origins of the “continuum of risk” theory

The idea that, " It's not the nicotine that kills half of all long-term smokers, it's the delivery mechanism" originated with Michael Russell in his 1991 paper "The future of nicotine replacement."¹³ Here is what Russell said:

Since people smoke mainly for nicotine and fail to quit because they are addicted, and since they die mainly from the tar, carbon monoxide and other harmful gases taken in alongside nicotine, and since they chew and snuff tobacco for nicotine but die largely from the nitrosamines and other carcinogens in tobacco, *it seems logical* to offer either a cleaner product or, better still, an acceptable source of purer, less contaminated nicotine. [emphasis added]

Note that Russell presented this idea as a *hypothesis*, not as established fact.

He then summarized the understanding of the biological mechanisms through which smoking causes cancer and heart disease:

Health risks of nicotine

While it is patently obvious that nicotine alone must be less harmful than nicotine plus tar plus noxious gases, decisions about policies for opening the market to cleaner nicotine replacement products and gradually phasing out tobacco will depend crucially on the health risks of nicotine. As mentioned earlier, it is assumed that there is no great objection to drug use and addiction per se. Nicotine addiction is not harmful. Unlike many other addictive drugs, nicotine does not disturb consciousness, impair judgement or social behaviour and, if anything, it enhances rather than impairs cognitive and psychomotor performance and the capacity to work. The key question is the extent to which nicotine or its metabolites contribute to the harmfulness of tobacco.

Nicotine has no role in tobacco-related cancers, which are responsible for 30% of all cancer deaths, neither is it implicated in chronic obstructive lung disease. The possibility of endogenous formation of carcinogenic nitrosamines from nicotine metabolites has been suggested (Hoffmann, 1989). However, it has not been demonstrated and, if it occurs, the amounts would be negligible compared with those present in tobacco and formed when it is burned. It is likely that nicotine is implicated in the cardiovascular risks of cigarette smoking and that carbon monoxide also plays a part. However, to date no definitive epidemiological studies have identified the cardiovascular risks of individual smoke components. Nicotine activates the sympathetic nervous system and increases circulating

¹² Mejia, et al. Quantifying the effects of promoting smokeless tobacco as a harm reduction strategy in the USA. *Tob Control* 2010;19:297-305 doi:10.1136/tc.2009.031427. (A copy of this paper is appended to this comment.)

¹³ Russell M. The future of nicotine replacement. *British J Addict* 1991;86:653-658.

levels of adrenaline, noradrenaline and vasopressin. Through these mechanisms it causes peripheral vasoconstriction and may also contribute to atherogenic and thrombogenic processes. It probably increases the adverse consequences of ischaemic heart disease. Propranolol largely abolishes the deleterious effects of smoking on mortality following a first heart attack (Jafri et al., 1990) indicating that adrenergic mechanisms are involved. This strongly implicates nicotine which is the only smoke component with effects on adrenergic systems.

In contrast with cigarette smoking, the cardiovascular risks are negligible in primary pipe and cigar smokers who have never smoked cigarettes and who tend not to inhale deeply (Doll, 1983). It is not clear whether the difference is due to the slower rate of buccal absorption from non-inhaled pipe and cigar smoking, to lower steady-state nicotine levels, or to lower CO levels. Similarly the lack of evidence that use of smokeless tobacco poses a cardiovascular risk is open to various interpretations.

In summary, nicotine has no part in tobacco related cancers and chronic obstructive lung disease, two of the major causes of tobacco-related premature deaths. There is some evidence that it contributes to the overall cardiovascular risks of smoking. These risks appear to be most evident when nicotine is rapidly absorbed through the lungs. However, it must be said that the evidence is discounted by two experts more competent than I am to assess it. They state: "That nicotine has a role in the cause of cardiovascular disease has its adherents, but the evidence is not compelling" (Froggatt & Wald, 1989).

While this was a reasonable summary of the evidence in 1991, **23 years ago**, it does not reflect important things that we now know about the mechanisms by which smoking causes disease and the adverse effects of nicotine:

- *There is a highly nonlinear dose-response for the effects of smoke exposure on cardiovascular disease risk, with large effects at low levels of exposure.*¹⁴
- *The ultrafine particles that cigarettes (and e-cigarettes) deliver have substantial adverse effects on the cardiovascular system.*¹⁵
- *Nicotine may not be a primary carcinogen, but has carcinogenic effects and likely promotes cancers once established through angiogenic (promoting growth of blood vessels in tumors) effects.*¹⁶
- *A dose of nicotine via nasal spray has the same immediate adverse effect on arterial function as smoking a cigarette.*¹⁷
- Nicotine is a reproductive toxicant.¹⁸

¹⁴ Institute of Medicine. Secondhand Smoke Exposure and Cardiovascular Effects: Making Sense of the Evidence. 2009. Also see Barnoya J, Glantz S. Cardiovascular effects of secondhand smoke: nearly as large as smoking. *Circulation* 2005 May 24;111(20):2684-98.

¹⁵ Institute of Medicine. Secondhand Smoke Exposure and Cardiovascular Effects: Making Sense of the Evidence. 2009. Also see Barnoya J, Glantz S. Cardiovascular effects of secondhand smoke: nearly as large as smoking. *Circulation* 2005 May 24;111(20):2684-98 and Grana RL, Benowitz N, Glantz SA. E-cigarettes: a scientific review. *Circulation* 2014 May 13;129(19):1972-86. doi: 10.1161/CIRCULATIONAHA.114.007667.

¹⁶ Grando SA. Connections of nicotine to cancer. *Nature Reviews Cancer* 2014; 14: 419–429. doi:10.1038/nrc3725 Published online 15 May 2014. See also Zhu BQ, Heesch C, Sievers RE, Karlner JS, Parmley WW, Glantz SA, Cooke JP. Second hand smoke stimulates tumor angiogenesis and growth. *Cancer Cell* 2003 Sep;4(3):191-6.

¹⁷ Neunteufl T, Heher S, Kostner K, Mitulovic G, Lehr S, Khoschorur G, Schmid RW, Maurer G, Stefenelli T. Contribution of Nicotine to Acute Endothelial Dysfunction in Long-Term Smokers. *J Am Coll Cardiol* 2002;39:251– 6.

While we cannot fault Russell for not anticipating these findings, these are well-established and biologically important effects that the FDA needs to integrate into its regulatory decision making.

Beyond Biology: The Cigarette Companies

When Russell developed his theory it was done completely in the context where the only product that the tobacco companies were promoting was cigarettes and the alternative was pharmaceutical nicotine in the form of NRT. Today the e-cigarettes are increasingly sold by the large cigarette companies for recreational use and to bypass smoking restrictions.

Profit maximizing behavior of the cigarette companies will dictate that they manage the e-cigarette market in a way that will maximize total profits, which will necessarily lead them to promote dual use and use of e-cigarettes to promote cigarette use and discourage quitting. The FDA cannot ignore these market incentives on the tobacco companies.

Indeed, the FDA must also remember, as Congress did when enacting the Family Smoking Prevention and Tobacco Control Act, that in August 2006 a United States district court judge found that the major tobacco companies “designed their cigarettes to precisely control nicotine delivery levels and provide doses of nicotine sufficient to create and sustain addiction while also concealing much of their nicotine- related research. *USA v. Philip Morris, USA, Inc., et al.* (Civil Action No. 99–2496 (GK), August 17, 2006).” (TCA section 2(49)) Those companies (Lorillard, Philip Morris, and Reynolds) have since entered the e-cigarette market and are also still selling cigarettes and other combustible tobacco products. These companies’ past racketeering activities provide ample reason for concern that they may be designing or manipulating e-cigarettes to similarly “precisely control nicotine delivery levels and provide doses of nicotine sufficient to create and sustain addiction.” Indeed, the “delivery mechanism” itself could be designed in a way to maximize these companies’ profits by controlling nicotine delivery levels to increase the likelihood that non-users will become users of nicotine, to decrease the likelihood that current users will stop using nicotine, and that e-cigarette and new product users will become dual users of both combustible and non-combustible products.

The consistent observation that adult smokers who use e-cigarettes are less likely to have stopped smoking than those who do not use e-cigarettes and the high levels of dual use¹⁹ is exactly the consumption pattern that one would expect to maximally benefit companies that sell both cigarettes and (less profitable) e-cigarettes.

In addition, the high levels of dual use of e-cigarettes and cigarettes, the fact that youth who experiment with e-cigarettes are 7.7 times more likely to become established smokers than youth who do not use e-cigarettes, and the fact that youth who use e-cigarettes are less likely to have ceased smoking than those who do not use e-cigarettes²⁰ all strongly suggests that e-cigarettes, as currently promoted, are leading to more smoking cigarettes.

¹⁸ US Surgeon General. *The Health Consequences of Smoking: 50 Years of Progress*. 2014 Chapter 5: Nicotine.

¹⁹ Grana RL, Benowitz N, Glantz SA. E-cigarettes: a scientific review. *Circulation* 2014 May 13;129(19):1972-86. doi: 10.1161/CIRCULATIONAHA.114.007667.

²⁰ Dutra LM, Glantz SA. Electronic Cigarettes and Conventional Cigarette Use Among US Adolescents: A Cross-sectional Study. *JAMA Pediatr.* 2014 Mar 6. doi: 10.1001/jamapediatrics.2013.5488. [Epub ahead of print]

The limitation on these data is that they are from cross-sectional studies, but, if e-cigarettes were discouraging smoking these results would be just the opposite.

In any event, the FDA will have longitudinal data on the behavioral linkages between e-cigarette use and cigarette use which will provide more information on these questions for both youth and adults, particularly the rate at which e-cigarettes act as a gateway for cigarette smoking and discourage quitting from its PATH study, which is now in the field. The FDA should not issue any regulations based on assumptions about harm reduction until the results of the PATH study (or other comparable data) are available.

Conclusion

FDA acknowledges (p. 23147) that “regulatory policy under the Tobacco Control Act must account for the *net public health impacts* at the population level. This includes impacts on initiation, cessation, and an evaluation of product harm.”

This public health standard means that the FDA is mandated to protect the public health by determining “with respect to the risks and benefits to the *population as a whole*, including users and nonusers of the tobacco product, and taking into account (A) the increased or decreased likelihood that existing users of tobacco products will stop using such products; and (B) the increased or decreased likelihood that those who do not use tobacco products will start using such products.” [TCA section 906(d)]

While there is no question that some adult smokers would be better off switching to e-cigarettes than continuing to smoke combustible cigarettes, the aggressive marketing of e-cigarettes to youth and the ubiquitous availability of appealing youth-friendly flavors (that the FDA does not propose to regulate, much less prohibit) make it more likely than not, to use FDA’s own words, that e-cigarettes “can introduce youth into a lifetime of addicted tobacco product use and related harms, including premature death” (p. 23146).

Therefore, until such time that there is a better understanding of the full health risks of using e-cigarettes (including cardiovascular and lung disease) together with affirmative empirical evidence that validates that e-cigarettes as actually used move the population down a theorized “continuum of risk,” the FDA should not base any regulatory decisions on this theory.