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Recommendations to FDA in response to the request for comment on proposed deeming regulations

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June 10, 2014

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Introduction and summary statement

This note is in response to the April 2014 FDA Docket No. FDA-2014-N-0189 requesting comment on proposed regulations for extending the authority of the FDA Center on Tobacco Products (CTP) to a number of tobacco products not covered by the 2009 Family Smoking Prevention and Tobacco Control Act (the Law).

FDA has proposed a set of regulations intended to bring almost all non-pharmaceutical, tobacco-related products under the authority of the CTP. This step requires CTP to demonstrate it has the authority and capability, within the current scope of its jurisdiction, to implement a regulatory structure that will protect and improve public health.

CTP's performance to date is very much open to question, given its failures to propose regulations governing the manufacturing quality of products already under its jurisdiction; to process thousands Substantial Equivalent applications; and to communicate practical guidelines to manufacturers for New Product, Reduced Exposure and Modified Risk applications. Substantially increasing the numbers of products the CTP will regulate could make matters worse.

As a public health physician, I strongly support FDA regulation of all tobacco and nicotine-delivery products, provided that regulation is evidence-based, practical and reasonably streamlined in a way that will protect and enhance public health. Unfortunately, it appears CTP is nowhere near meeting this performance standard. The 24-month grace period built into the currently proposed deeming regulations may help sort out these internal problems, but there is nothing in the proposal that indicates CTP recognizes the problems exist.

Though I have no direct insight into the inner workings of CTP, their paralysis appears related to an unwillingness or inability to acknowledge that approval guidelines will expose the public to some degree of risk. This reluctance is compounded by substantial discrepancies between prescriptions in the text of the Law and what our "evidence base" suggests should be done to protect and improve public health.

As I see it, the discrepancies are so severe that, if CTP opts to implement the letter of the Law without administrative discretion to accommodate contrary evidence, FDA efforts will do more harm than good in terms of future rates of tobacco-related addiction, illness and death in the United States.

I respectfully urge FDA to consider alternate approaches in pursuit of public health objectives. After determining which approaches comport with our best evidence, the agency then could consider which actions would fall within a reasonable scope of administrative discretion, and which, if any, might require technical corrections by Congress.

In the best of all worlds, CTP would suspend further consideration of the proposed deeming regulations until it can demonstrate to Congress, industry and the general public that it is successfully executing its existing responsibilities. Only then should it proceed to release an amended set of deeming regulations for public comment.

Suspecting that this will not be done, I offer the following observations and recommendations.

These recommendations are largely based on the "continuum of nicotine delivery products." They represent one public health physician's opinion on best how to streamline the FDA regulatory process; bring it in line with the totality of scientific evidence, as opposed to research limited to each newly proposed product; and pave the way for substantial reductions in tobacco-related harms in the United States.

The tobacco control law was intended to reduce tobacco-attributable addiction, illness and death, while allowing adults who choose to do so to continue use of tobacco and non-pharmaceutical nicotine-delivery products. The law was not intended to eliminate such products from the American marketplace by imposing regulatory burdens so onerous that none but the largest of the "big tobacco" companies could comply.

Unfortunately, the Law includes a number of provisions that directly conflict with the evidence base. Discrepancies between the Law and the evidence base include, but are not limited to the following:

1) Risk to non-users is based on the physical and chemical characteristics of the product, without regard to marketing or social factors;
2) The presumption that fruit and candy flavors other than menthol are intended to attract children and teens to tobacco use, and that such flavoring is not required to make the lower-risk smokeless and nicotine-only products palatable to adult users;
3) The presumption that any statement of reduced exposure or reduced risk is likely to attract large numbers of teens and other non-smokers to nicotine use;
4) Emphasis on chemical analyses as a means of ascertaining the risk posed by a tobacco product, without regard to the lack of certainty regarding how much cancer, heart, lung and other disease risks can be attributed to any given chemical substance;
5) Disregard of the American and Scandinavian epidemiologic literature demonstrating major difference in risk between cigarettes and smokeless and other tobacco and nicotine-only products.

Because of these discrepancies, proceeding further with implementation of the Law without due exercise of administrative discretion may do more harm than good, in terms of our collective ability to reduce tobacco-related addiction, illness, and death in the United States.

The Law, and CTP implementation to date, both appear to presume that each newly proposed tobacco product is so unique that research findings on similar products cannot be considered. This presumption so substantially increases the cost and difficulty of New Product applications that none have been fully submitted to date. This presumption also substantially increases the burden of processing such applications and denies FDA use of prior literature for baselines and benchmarks with which to judge such applications. The stakeholders who benefit from this presumption are those in the tobacco control community who would prefer to eliminate all tobacco and non-prescription nicotine delivery products, as well as the cigarette and pharmaceutical companies who would like the Law to protect them from competition from

relatively low-risk smoke-free and nicotine-only products. However, the presumption does nothing to protect or enhance public health.

Fourteen specific recommendations are listed at the end of this report. Most, if not all, of them can be implemented without congressional action. Where congressional action is required to bring the Law into better concordance with congressional intent, such action should be requested.

Basic principles underlying these recommendations:

The following principles are based on a much wider range of scientific literature than envisioned in the proposed FDA regulations.

1) Nicotine is the primary addictive substance in tobacco products, but it is other toxic substances in tobacco smoke that cause almost all serious illness and death in the United States.{SurgGen 2014} The cigarette is the sole product responsible for all of the 480,000 deaths per year in the United States attributed to tobacco use by CDC. {cdc 2013 TobcMort; SurgGen 2014} The number of deaths from all other tobacco products combined are so small and so hard to discern from background statistical noise that they are not tracked or estimated by CDC. Meanwhile, the nicotine-only products licensed by the FDA as pharmaceuticals are considered so safe that, beginning in April 2013, they were approved by FDA for unlimited use as to dose and duration, even while users continue to smoke.{ FDA 2013 NRT Notice}
2) Nicotine is particularly harmful to children, adolescents, young adults up to age 25 and pregnant women.{SurgGen 2014: SAMHSA 2013 5.7}
3) There is a well-established continuum of risk of potentially fatal cancer, heart, lung and other diseases in which cigarettes are the most hazardous cause, followed by other combustible tobacco products, smokeless tobacco products and, finally, nicotine-only products, such as pharmaceutical nicotine replacement therapy (NRT) patches, gums, etc, and, more likely than not, e-cigarettes.{SurgGen 2014; Rodu 2011 8; Lee 2013 36}
4) The major exception to this rule is a family of smokeless products that contain tobacco and other ingredients, widely used in Asia and other foreign markets, but not in the United States. These are the products most commonly referred to as gutka and pan masala with tobacco. These smokeless products appear to present a risk of potentially fatal tobacco-attributable illness similar to the risk posed by cigarettes.{ Gupta 2003 419} Since they are not readily available in the United States, they should not be used as basis for mandated warnings in the United States or for projection of future rates of illness and death in the United States.
5) Just as there is a continuum of risk, there is a corresponding continuum of addictiveness, with cigarettes having the strongest potential addictiveness and pharmaceutical NRT products having the least.{Fagerstrom 2013 520}
6) Propensity to nicotine addiction is based on the following major factors:
    1. Experimentation and initiation of tobacco use is largely dependent on marketing, peer and social pressure.{ SurgGen 2014}

2. Whether an individual continues tobacco use will depend on these same factors, plus tolerance to the product and whether the user senses any benefit from its use{ SurgGen 2014}
3. Whether repeated use becomes habituation or addiction will depend on the strength of the urge to use the product and how one feels if the urge is ignored. This tendency to addiction appears to be strongest with cigarettes, where habituation to the cigarette handling ritual and other potentially addictive substances in cigarette smoke may be significant factors.{Fagerstrom 2013 520}

7) Experience to date with e-cigarettes clearly demonstrates that smokers can be attracted to the products, without attracting teen or adult non-smokers, by the unrestricted availability of flavors and by knowledge that e-cigarettes pose far less risk than cigarettes.{CDC 2013 NYTS; ASHGB 2013 EcigUse; Siegel 2013 0930; Siegel 2013 0909; ASHGB 2014 EcigUse; Siegel 2014 0107 gateway} Thus, the presumption that candy and fruit flavors{Farsalinos 2013 272} and claims of reduced risk will attract large numbers of non-users should not govern tobacco control policy.
8) Our knowledge of the level of risk posed by the different categories of nicotine delivery products comes entirely from long-term epidemiologic studies.{ Rodu 2011 8; Lee 2013 36}
9) As defined in the epidemiological studies, within each category of tobacco products that have been widely available on the American and Scandinavian markets since the 1980s, we have no evidence that any given product poses a greater or lesser risk of any disease, condition or overall morbidity or mortality than the average for that class.
10) We have no idea how much of the potentially fatal illness from cigarettes or any other tobacco product can be attributed to any given chemical substance in the chemical or smoke. Moreover, there is no research methodology that would enable us to make any such determination reliably. The one research study I am aware of that attempted to make such estimates (Pankow 2007) estimated that elimination of the most prominently mentioned carcinogens in tobacco smoke would reduce the risk of lung cancer by less than 4 percent.{ Pankow 2007 584}
11) The differences in risk of potentially fatal illness posed by the different classes of tobacco products appear to be almost entirely due to the differences in the way the person using the product is exposed. Burning tobacco creates both gaseous and tarry products of combustion that are inhaled deeply into the lung, with cigarettes inhaled most deeply. The further the toxins enter the lungs, the more the gaseous substances are likely to be absorbed and the more likely tarry residues are to stick in place. These processes result in long-term exposure. Cigars and pipes are not usually inhaled as deeply, and therefore convey less risk. Smokeless tobacco products are not inhaled at all. They mainly expose the oral mucosa, a less delicate surface than the pulmonary alveoli. The nicotine-only products likely convey even less risk, having eliminated all but the tiniest traces of other tobacco-related toxins.
12) At the risk of considerable oversimplification, the epidemiologic findings can be described as follows:
    1. When consistently used over a period of years, cigarettes kill one-third to one-half of consistent users, with the risk dependent on pack-years of use and host factors.{ cdc 2013 TobcMort; SurgGen 2014}

2. Pipes and cigars probably pose a risk equivalent to 20 percent to 100 percent of the risk posed by cigarettes.**** This difference in risk, while not insignificant, pales in comparison to the reduction in risk offered by smokeless options and nicotine-only products. The 100 percent risk is intended to reflect the likely risk posed by small cigars and cigar-like products that are really cigarettes in disguise.
3. Hookahs, shishas and water pipes are poorly studied epidemiologically, because there are so few users who do not also smoke cigarettes. Given what we know, it appears they likely pose a risk as high as cigarettes, due to the inhalation of the fumes of burning charcoal and extreme exposure to carbon monoxide. Charcoal fumes contain an array of carcinogens and other toxins, similar to those found in tobacco smoke.{Monzer 2008 2991; Eisenberg 2009 518}
4. Chewing tobacco, snus and other smokeless snuff products that have been on the American and Scandinavian markets since the 1980s pose a risk of potentially fatal illness less than 2 percent of the risk posed by cigarettes.{Rodu 2011 8; Lee 2013 36}
5. Dissolvables (sticks, strips and orbs) and e-cigarettes are too new to have been subject to long-term epidemiologic study. They almost certainly pose even less risk than the unrefined whole-tobacco smokeless products noted above. A good guess might be a risk less than 0.1 percent the risk posed by cigarettes. That is a guess, based on experience to date with pharmaceutical nicotine replacement therapy (NRT) products.
6. The NRT products have been in common use since the 1980s and have been extensively studied. There is nothing in the literature alleging any increased risk of potentially fatal tobacco-attributable illness due to use of these products.{ FDA 2013 NRT Notice}

There are significant numbers of people in American society who gain substantial benefit from self-administered nicotine. These include, but are likely not limited to, persons with schizophrenia, depression and/or bipolar disorder.{ Kumari 2005 1021; Sacco 2005 649; Wing 2011 320; Houezec 2014 0112} This phenomenon needs to be formally recognized by the tobacco control community and incorporated into their policies and programming. For these individuals, THR utilizing a relatively low-risk smokeless or nicotine-only product is likely to be a better option than total cessation of nicotine use.

Implications of these basic principles for FDA regulation and overall federal tobacco-control policy

Classification of tobacco-related Products

The first step should be to sort tobacco products by class, determining the regulatory approach for each class and how differences in risk are to be communicated to the public. Whether this is a simple two-class scheme (combustible/smokeless) or a more elaborate scheme (Cigarette, other combustible, smokeless, e-cigarette, NRT) will be a matter for further consideration.

Producers of each class of products would be authorized to communicate the difference in risk and addictiveness, compared to cigarettes, as best such differences can be ascertained.

The requirements for reduced exposure and reduced risk designation specified in Section 911 of the Law would be reserved for those manufacturers who wish to claim their product is at least one order of magnitude (10x) lower in risk than others within that class of product.

The stringency of the requirements, marketing guidelines and the difficulty of the application process each should reflect the level of risk posed by the class of product and any claims the manufacturer might wish to make comparing their product to others within the class.

Marketing and mandated warnings

The ban on sales to minors should be implemented and strictly enforced for all tobacco and non-pharmaceutical nicotine delivery products.

Use of image-based, symbolic and psychological themes should be prohibited for all products. Co-branding of non-tobacco products and visible event sponsorship should also be banned.

Restrictions on marketing on cigarettes should be imposed on all combustible products. For the smokeless and nicotine-only products, manufacturers and vendors should be allowed to communicate the difference in risk compared to cigarettes. Television advertising should be allowed for the lower-risk products, but not for the combustibles.

To pave the way for a more rational approach to the smokeless and nicotine-only products to be deemed, the warnings mandated for smokeless tobacco products, as written into the Law, need to be reconsidered. Only the warning relating to potential addiction is accurate as written. The other three (cancer, tooth and gum disease, and "not a safe alternative" to cigarettes) are grossly exaggerated.{Rodu 2011 8; Lee 2013 36} and have served to convince both physicians and the lay public that these smokeless products pose a risk of potentially fatal tobacco-attributable illness equal to the risk posed by cigarettes.{ Borland 2011 821; OConnor 2007 1033} These warnings appear to have been put into place on the basis of international data, which, in turn, reflects the hazards posed by gutkha and pan masala with tobacco – products not readily available on the American market.{Gupta 2003 419}

Flavoring

Given the harsh taste of nicotine, sweetening or other flavoring is needed to make smokeless and nicotine-only products palatable to potential adult users.{ Farsalinos 2013 272} For these products, a ban on flavoring would be a de facto ban of the products themselves.*****

Combustible products present a different picture. Small amounts of menthol and other additives and use of tobacco blends with higher sugar content can be used to soften the taste without imparting a "characterizing" flavor.

It is important to note that there are no sales or usage data showing that fruit and candy flavors other than menthol ever attracted large numbers of minors to smoking.***** For all practical purposes, these other flavors were already removed from the market prior to the introduction of

the Law, because so few people were buying them. It seems unlikely that any of the cigarette companies care whether this ban remains in place.

Toxicology, chemical analysis and quality of manufacturing

Product label references to specific chemical substances, intended to enable consumers to compare products on the basis of their chemical components, should be abandoned as fraudulent. Eliminating this requirement may require amendment of the Law.

The principle uses of chemical analyses of tobacco products should be to assure the quality and consistency of the product, freedom from "filth and adulteration" and freedom from products of decomposition.

New Product and Substantial Equivalence applications

There should be only three substantial "questions of public health." These are:

1) Risk to users
2) Quality and consistency of manufacturing relative to the dose of nicotine, "filth" and "adulteration;"{FDA Tobc Law}
3) Risk of recruitment of non-users to nicotine addiction and/or eventual cigarette smoking.

Each of these comparisons should be made to other products within the same class. Requirements for chemical analysis should be limited to the issues noted above. Risk to users and non-users should be primarily addressed through marketing restrictions, on the concentration of nicotine and anticipated efficiency of nicotine delivery.

Decisions about whether allowing a given product on the market will serve public health should be limited to eliminating products that present new or unusual types or levels of risk. Banning products for other reasons would stifle continuing product improvement, especially for e-cigarettes, dissolvables and other relatively low-risk products.

These changes from current practice should enable FDA to rapidly clear the backlog of Substantial Equivalence applications and simplify and reduce the cost of both New Product and Substantial Equivalence applications for both manufacturers and FDA.

Regulation of e-cigarettes

E-cigarettes present a special set of regulatory issues not presented by any other tobacco related product. E-cigarettes do not contain tobacco. They contain nicotine, derived from tobacco. They also represent a rapidly evolving technology with thousands of manufacturers in the marketplace and many users actually manufacturing their own fluids and devices. The technology, as it has evolved over the past eight years, has resulted in products that are both safer and more effective than prior generations of e-cigarettes. Thus, it would not be beneficial for FDA to impose a regulatory scheme that would stifle further innovation.

E-cigarettes vaporize a nicotine-containing liquid for the purpose of satisfying the urge to smoke without the myriad toxins present in cigarette smoke. The fluid is a conceptually simple mixture of no more than six ingredients: nicotine, propylene glycol, vegetable glycerin, citric acid, distilled water and flavoring.{AEMSA 2014 0114; Siegel 2014 0606} The critical specification for the device is the temperature of the heating element, so that it gives the desired nicotine and vapor without heating the fluid so much that significant quantities of formaldehyde and other toxins are created. The quality of the battery is also an issue, since there have been reports of exploding batteries.

Given these circumstances, it should be possible to develop a regulatory scheme along the following lines:

1. The quality and consistency of e-cigarette fluid could be controlled by insisting that each of the ingredients meet the USP standard and the guidelines of the American E-Liquid Manufacturing Standards Association.{AEMSA 2014 0114} These include a requirement that refill liquids be packaged in child-proof containers.
2. Quality and consistency standards can be implemented for batteries, heating elements and temperature control.
3. For the "vape shops" that custom-make e-cigarette devices and fluid mixtures to meet the needs of individual vapers, requirements for licensure, sanitation and training of compounders can be implemented.
4. Marketing and allowable-vendor communications can be similar to new guidelines for chewing tobacco, snus, snuff and dissolvables, provided the technically inaccurate and misleading warnings now mandated for the smokeless products are eliminated.

Pharmaceutical nicotine replacement therapy (NRT) products

NRT products should face the same marketing restrictions as lower-risk smokeless and nicotine-only non-pharmaceutical products. NRTs also should be covered by the same surveillance systems that cover all other non-pharmaceutical tobacco and nicotine-only products. NRTs are the nicotine products currently most accessible to children and teens. They are available on open store shelves, in candy and fruit flavors, without enforced age restrictions. We have no data on the extent to which these products are used by teen smokers or abused by teen non-smokers, because no tobacco-related surveillance system currently covers this family of products. Whether sales of these products should be prohibited for persons under 18 would depend on the findings of surveillance efforts.

Surveillance

FDA, CDC, SAMHSA and possibly NIH should collaborate on a range of better-coordinated surveillance efforts to determine usage of all classes of tobacco products, including NRTs and contraband. Surveillance systems would help ascertain the driving factors behind usage and the benefits and harms attributable to each product class. The results would enable each of the participating federal agencies to make mid-course corrections of policy and programming, as appropriate, to enhance public health.

Contraband

Mandated product modifications or removal of desired products from the market is almost guaranteed to generate a black-market response. FDA should play a lead role in researching and implementing protocols to identify and eliminate contraband.

Tobacco harm reduction as public health policy

Tobacco harm reduction (THR) should be implemented as a supplement to current tobacco-control programming where it has the potential to reduce tobacco-related illness and death. To maximize THR's benefits to current smokers, without recruiting additional teens to tobacco use, will require collaboration with manufacturers and vendors on marketing practices. It also will require re-orientation of that portion of the tobacco control community whose goal long has been pursuit of a "tobacco-free society." For some, this goal has precluded any consideration of non-pharmaceutical tobacco product options in the context of any public health initiative.

Restatement of public health goal

The most important single step to enhance our collective ability to reduce substantially tobacco-related harms in the United States will be to restate the goal of tobacco control from "a tobacco-free society" to "a smoke-free society, virtually free of tobacco-related illness, death and addiction."

Recommendations to FDA for Revision of the Proposed Deeming Regulations

1. Based on experience to date with e-cigarettes, the presumption that the availability of candy and fruit flavors and claims of reduced risk will attract large numbers of teens and other non-users to tobacco use should no longer be used as a guideline governing development of tobacco control policy.
2. Institute a classification scheme for tobacco and nicotine-only products based on the epidemiologic data showing differences in risk and addictiveness between classes of tobacco and nicotine-only products, relative to cigarettes.
3. Provide different marketing, flavoring and toxicological guidelines for each major class of tobacco and nicotine-only product.
4. Allow smokeless products and e-cigarette products to claim lower risk than cigarettes, based on class of product, as noted above.
5. Reconsider the warnings now mandated for smokeless tobacco products, based on epidemiologic data published in the past thirty years.
6. Do not restrict flavoring options for other classes of tobacco and nicotine-only products.
7. Restrict requirements for toxicological analyses to those that can be verifiably related to the risk of potentially fatal tobacco-attributable illness and/or to quality of manufacturing.
8. Regulation of e-cigarette manufacturing should not stifle continuing product development. FDA standards should be limited to the quality of ingredients used for e-cigarette liquid; safety, as specified by the American E-Liquid Manufacturing Standards Association; {AEMSA 2014 0114} standards for batteries; and performance standards for the heating element and temperature control.

9. Extend, by whatever means, guidelines and requirements relative to marketing and flavoring to the nicotine replacement therapy (NRT) products regulated by the FDA Center for Drugs and Research (CDR).
10. FDA should play a lead role in expanding and coordinating tobacco-related surveillance systems run by other federal agencies to include coverage of NRT products, better ascertain the determinants of use of various tobacco products and to gauge their impact on the community.
11. FDA should play a lead role in identifying and eliminating contraband tobacco and nicotine-only products from the American marketplace.
12. FDA should play a lead role in incorporating a tobacco harm reduction (THR) component to tobacco control programming.
13. FDA should play a lead role in restating the goal of American tobacco control efforts from "a tobacco-free society" to "a smoke-free society, virtually free of tobacco-related illness, death and addiction."
14. If needed, petition Congress to amend the Law to enable implementation of the recommendations noted above.

About the Author:

Joel L. Nitzkin, MD. MPH. DPA is a public health physician, board certified in Preventive Medicine. He has been a local health director, state health director, President of two national public health organizations and participant in multiple federal advisory panels. He started his public health career as an EIS officer, and, for decades after, considered the CDC his professional home away from home. He has been actively involved in tobacco control since the early 1970's. His foray into tobacco harm reduction began in February 2007, when the FDA tobacco bill was introduced into Congress. In his then-current-capacity as co-Chair of the Tobacco Control Task Force of the American Association of Public Health Physicians, he was one of an AAPHP team that downloaded and read through the entire bill so we could advise AAPHP regarding endorsement. They were appalled at the pro-Altria, pro-pharmaceutical industry, anti-public-health provisions written into the law. This, in turn, led to their own literature search and analysis to ascertain what AAPHP, as a group of public health physicians, could recommend as to optimal tobacco control policy in pursuit of public health objectives. This search, in turn, directed their attention to the potential public health benefits of tobacco harm reduction, and how it might be done while minimizing, if not reducing teen initiation of tobacco/nicotine use. All this – before they were aware of e-cigarettes.

To enable travel and coverage of other expenses for him to continue work in this arena, He sought support from a neutral source. Thus, his affiliation with the R Street Institute. R Street is a Washington-based think tank that respects the role of government in regulating industry to protect health and safety, but strongly opposes excessive government interference in the market place. FDA's unsuccessful attempt to remove e-cigarettes from the marketplace by declaring them to be drug-device combinations brought this issue to their attention.

Dr. Nitzkin has never sought nor secured any support from a tobacco company, e-cigarette company or pharmaceutical firm.