Comment on Docket No. FDA-2015-N-2002 relative to when tobacco-related products should be regulated as drugs, devices or combination products

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Summary Recommendations:

1. FDA should redefine smoking as a behavior, not a disease, and regulate all tobacco-related and nicotine delivery products accordingly.

2. FDA should migrate all regulation of tobacco-related and nicotine delivery products to the Center for Tobacco Products (CTP), with the partial exception that those choosing to be marketed as drugs must also meet the safety, efficacy, research and documentation requirements of the Center for Drug Evaluation and Research (CDER).

3. If implementation of these recommendations is deemed inconsistent with the current text of the FDA tobacco law[1] action should be taken to amend the law as needed to implement these recommendations for the purposes articulated in this Comment to FDA.

Introduction:

The current division of regulatory responsibility between the FDA Center for Tobacco Products (CTP) and the Center for Drug Evaluation and Research (CDER) has fostered a dysfunctional and scientifically unsound regulatory process by which tobacco products regulated by CTP are deemed to have harms, but no potential benefits, and products regulated by CDER are deemed to be unattractive to teens and other non-smokers, safe, and effective, no matter how strong the evidence to the contrary.

E-cigarettes and related vapor devices (e-cigs) are most likely responsible for the recent record reductions in both teen and adult smoking in the USA,[2,3] UK,[4,5] and Poland.[6] These data are fully consistent with the hypothesis that most, if not all of the major reductions in cigarette use by teens are most likely due to the ever-increasing popularity of e-cigarettes for both current smokers and potential smokers experimenting with tobacco-related products. The fact that this same phenomenon is being observed in three very different countries with very different cultures and regulatory environments further supports the premise that these record reductions are, indeed, due to the skyrocketing use of e-cigs.

Despite this evidence, public health authorities continue to condemn e-cigarettes. FDA has even proposed deeming regulations, which, if implemented, would likely eliminate

the entire American e-cig industry by imposing requirements that would be physically impossible for any e-cig manufacturer to meet in the context of a pre-market application. This action, if successful, could reverse the recent record reductions in both teen and adult smoking.

The implications of FDA continuing to think of smoking as a disease are substantial. The current situation is one in which CTP thinks only in terms of potential harms of tobacco related products, and CDER only considers benefits that can be documented by means of randomized clinical trials of individual substances to secure short-term smoking cessation. This leaves no place within FDA to consider benefits such as harm reduction and population health impacts that cannot be addressed by randomized clinical trials. This leaves no place within FDA that can consider benefits of a class of products, rather than one stock keeping unit (SKU) product at a time. Reframing smoking as a behavior, not a disease, and placing all regulation of all tobacco-related products in a single center with the flexibility to design and research and evaluation studies other than randomized clinical trials is a necessary first step if we are to ever enjoy the benefits that THR can offer.

The only partial exception to this rule would be to allow manufacturers who desire to market their nicotine delivery products as drugs to continue do so. Those who chose this option should also be required to meet all CTP requirements relative to marketing, impact on users and non-users, post-market surveillance, etc. This partial exception envisions regulation by CTP with CDER oversight to assure their requirements have been met.

Tobacco Harm Reduction (THR)

Tobacco harm reduction (THR) holds the promise of substantial reduction in cigarette consumption not likely achievable by any other means.[7-10] THR means encouraging smokers who are unable or unwilling to quit, to switch to far less hazardous and less addictive alternate nicotine delivery products. THR also implies diversion of potential smokers to far lower risk and far less addictive products, even including zero-nicotine e-cigs.[3,11] These are population health benefits that CEDR cannot address by means of randomized controlled trials. Confirmation (or lack thereof) could be addressed by CTP, with the freedom to do whatever surveys or other studies may be appropriate to confirm or deny these impressions.

As previously noted, a strong case can be made for the proposition that the dramatic decreases in teen smoking these past five years are mostly or entirely due to teen smokers switching to e-cigs in the USA, Great Britain, and Poland. Teens who otherwise would have initiated cigarette use are also being diverted to e-cigs, or abstinence from nicotine after experimenting with e-cigs.[2,3] This case is based upon dramatic increases in e-cig use by teens, concurrent with the reductions in smoking. The fact that tobacco control authorities simply refuse to consider this possibility[2,3,12,13] does not rule it out. These are population health benefits that CEDR cannot address by means of randomized controlled trials. Confirmation (or lack thereof) could be addressed by a CTP, with the freedom to

do whatever surveys or other studies may be appropriate to confirm or deny these impressions.

Adding a THR component to current tobacco control programming has the potential to secure public health benefits not otherwise achievable.[4,7,9,14] The anticipated benefits are two-fold. First is the reduction in risk of potentially fatal cigarette-attributable illness, well in excess of a 95% reduction.[15] Second is the overall reduction in non-smoker recruitment to nicotine use.[4,16-19]

The major theoretical downside to THR is fear that such an admission would result in recruitment of large numbers of teen and other non-smokers to nicotine use, and, once addicted, that they would then transition to cigarette use. As previously noted, in the case of e-cigs, this has simply not occurred to date. Given the dynamics by which this has not occurred, it seems reasonable to project that this will not occur in the future, even in the absence of federal regulation.

Historical Context:

Historically, the decision to regulate pharmaceutical nicotine replacement therapy (NRT) products as drugs most likely reflected a marketing decision by the drug companies based on the expectation of greater profits by marketing them as prescription drugs. We now find ourselves hostage to this marketing decision, made about forty years ago. At that time no one was thinking about THR or urging smokers to switch to less addictive and far less hazardous tobacco-related products.

Our long-term experience with NRT products over the past thirty-some years has been dismal. While touted as "highly effective" on the basis of clinical trials showing a short-term doubling or tripling of quit rates from about 3% to about 6-8%, these products consistently fail over 90% of smokers who used them as directed, even under the best of study conditions, when results are measured at six to twelve months.[20] They show no increased abstinence from smoking when results measured at 20 months.[20] As best we can tell, there have been no population-level reductions in prevalence of smoking attributable to NRT despite decades of reliance on these products for smoking cessation.[21] The reasons for this dismal performance seem fairly obvious. The products are over-priced, under-dosed and unsatisfying to most smokers. The idea of a short course of a smoking cessation product permanently eliminating the urge to smoke is unrealistic.

The current FDA regulatory framework has been shaped more by political and legal concerns than by public health science. The FDA tobacco bill was negotiated in secret by representatives of Altria and Tobacco Free Kids, both of whom felt that their interests would best be protected by preventing entry of any new products into the market, and by imposing major barriers to any product claiming less risk than cigarettes.[22] Amendments to the bill that might strengthen it from a public health perspective were ruled out of hand on the basis that any such amendment might induce Altria to pull its support from the bill.[22,23] Once adopted, the science and regulatory agenda of CTP was formulated in

response to the text of the bill without consideration of whether or not such formulation made any sense from a public health perspective.[24]

Whether or not FDA has the discretion to adopt the policy guidelines recommended herein is yet to be determined. If the determination is made that adopting these guidelines would require amendment of the FDA tobacco law, action should be taken to amend the law as needed to enable FDA and other federal agencies to more effectively reduce tobacco-related addiction, illness and death in the USA.

Nicotine Replacement Therapy (NRT) Pharmaceuticals:

Nicotine is far less addictive than cigarette smoke, as evidenced by the use of nicotine in the NRT products to wean smokers off smoking, and as evidenced to date by experience with e-cig products.[2,3] Despite comments to the contrary by tobacco control authorities,[12,13] nicotine is regarded by FDA as innocuous, as evidenced by the lack of any cigarette or tobacco-like warnings on pharmaceutical NRT products.

The CDER process for evaluation and regulation of NRT products has never served us well from a public health perspective. The CDER process has resulted in erroneous promotion of the NRT products as "highly effective," despite the fact that the NRT treatment protocols, even under the best of study conditions, have consistently failed over 90% of smokers when results have been measured at six to twelve months.[20] Despite decades of extensive use, the NRTs have had no measurable public health impact.[21]

Subjecting the NRT products to CTP marketing and other guidelines will eliminate the current loophole by which NRT products are sold over the counter in fruit and candy flavors, on open shelves, without age restrictions on sale. This current loophole has created a situation in which NRTs are the nicotine delivery products most accessible to teens. We have no idea as to the extent to which NRTs are attracting non-smoking teens to nicotine use because NRTs are not tracked by any federally sponsored surveillance program. None are subject to state and local level restrictions on sale of tobacco related products.

Current Tobacco-Related Regulatory Practices: CTP and CDER

The current division of regulatory authority between CDER and CTP is based on the false premise that smoking is a disease, not a behavior. This, in turn, has created the perception within FDA and by some tobacco control advocates that there can be no possible benefit to nicotine delivery products not licensed as a drug. It has also created the false perception that tobacco-related products licensed as drugs have no potential to recruit non-smoking teens to nicotine addiction.

Blinded and randomized clinical trials to determine the safety and efficacy of a drug are not suited for the determination of the safety and efficacy of using e-cigs in a THR mode. There is no way such a trial could be blinded. Randomization and limitation of the trial to

a defined e-cig product denies the participants the ability to select their preferred flavors and strengths of nicotine and change them at will. While CDER is not in a position to assess the safety and effectiveness of tobacco-related products in a manner far different from the way it assesses drugs used to cure disease, CPT should be free to develop whatever survey, surveillance and other research may be needed to most effectively assess and regulate the manufacture and marketing of e-cig, smokeless and other relatively low risk products.

Managing Smoking as a Behavior:

Some smokers are addicted to cigarette smoke.[25] Others are dependent on self-administered nicotine to quiet the noise in their head so they can be productive on the job and enjoy life.[26-29] Yet others simply enjoy the taste and feel of a cigarette.[30]

Reframing tobacco control from treatment of a disease to changing behavior would likely yield substantial public health benefits. It would encourage smokers to switch to far lower risk and less addictive products. It would facilitate smoking cessation and likely future nicotine cessation[31] It would also reduce the frequency with which teens experimenting with tobacco-related products continue into nicotine addiction. Current public health initiatives designed to leave the impression that vaping may be more hazardous than smoking discourage smokers from quitting and does nothing to reduce teen experimentation with tobacco related products.

Managing smoking as a behavior will enable CTP to develop the surveillance, survey, and other research and evaluation tools needed to document and track the full array of actual and theoretical benefits and harms presented by each class of nicotine delivery product.

Managing smoking as a behavior will also allow of how to best manage marketing, packaging and product placement to attract current and potential smokers while minimizing recruitment of non-smokers. This will avoid the current process by which restrictions on flavoring and strength of nicotine are proposed that would make e-cigs less attractive to current smokers while doing nothing to reduce recruitment of non-smokers.

E-Cigarette Issues

Two recent studies show that the more sophisticated vapor products available from vape shops are far more effective in getting smokers to switch, to reduce cigarette consumption and to eventually quit than the mass-marketed standardized cig-a-like products.[31,32] Optimizing the potential benefits e-cigs can offer will require a regulatory regimen that will allow and encourage such flexibility in product design and encourage continuing product innovation. The current CDER process does not allow such flexibility. CPT could develop a regulatory process that could do so.

The e-cig line of products are intended by manufacturers and vendors to be recreational alternatives to cigarettes to enable smokers who have been unable or unwilling to quit to continue nicotine use while substantially reducing their risk of potentially fatal cigarette-related illness. They are used in this manner by the vast majority of e-cig users. Allegations that e-cigs are intended to recruit teens and other non-smokers to nicotine addiction do not reflect the thinking, actions or intentions of the e-cig manufacturers, vendors and users. The advertising and flavoring frequently referenced as directed toward minors is, in fact, advertising and flavoring intended to attract and retain young adults and other e-cig users.[33,34]

Even with unrestricted marketing, fruit and candy flavors and access to high levels of nicotine, e-cigs have not attracted significant numbers of non-smoking teens or other non-smokers to either nicotine addiction or to cigarettes.[2,3] In fact, a strong case can be made for the proposition that most, if not all of the decrease in prevalence in teen cigarette use is due to teen smokers switching to e-cigs and to teen non-smokers being diverted from cigarette use through experimentation, most commonly with zero-nicotine e-cigs.[2,3]

CTP takeover of the entire regulatory process would enable CTP to address the following:

1. To attract the maximum numbers of smokers to quit, e-cigs and smokeless products should be framed as low risk alternatives to smoking.

2. The tobacco harm reduction (THR) process is longer and slower than a short course of a medication to treat an acute disease. It is also highly variable from smoker to smoker as to the rate with which they cut down and eventually quit.

3. The current pharmaceutical nicotine replacement therapy (NRT) process shows high levels of abstinence which rapidly fall off over time.[20] The e-cig process is one in which abstinence rates increase over time.[35]

4. Promoting e-cigs for THR (as opposed to medical treatment for a disease) has been shown to recruit smokers who do not see smoking as a disease and who have no interest in quitting.[35]

5. The e-cig THR process appears to work best where the smoker can choose the flavor and strength of nicotine and change it at will over time as they become accustomed to the process and wean themselves off cigarettes, and, eventually, off nicotine.[31,32]

6. While e-cigs have attracted many non-smoking teens to experiment with these products, very few have continued to consistent nicotine use and almost none to cigarettes.[4,36,37]

7. Most teen experimentation with e-cigs are with zero-nicotine products.[3,11] While not technically under FDA jurisdiction, comprehensive regulation of e-cigs under a single FDA center would facilitate recognition of this phenomenon in regulation and in public health programming.

8. None of the THR-related issues noted above have been addressed by FDA to date. The mindset imbedded in FDA thinking under the current regulatory arrangement appears to be to the effect that that no tobacco-related product can possibly offer benefits if it is not licensed as a drug. CTP has not investigated these issues because they only consider potential harms. CDER has not investigated these issues because they are not considered drug benefits. This is despite the fact that THR remains the most promising policy option for future reductions in tobacco-related addiction, illness and death.

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