February 2, 2018

Commissioner Scott Gottlieb, MD
c/o Division of Dockets Management
HFA-305
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20825

Re: Review of Existing Center for Tobacco Products Regulatory and Information Collection Requirements

Docket No. FDA-2017-N-5095

Dear Commissioner Gottlieb:

The Public Health Law Center is pleased to submit these comments to the U.S. Food and Drug Administration (FDA) on existing Center for Tobacco Products Regulatory and Information Collection Requirements. The Public Health Law Center is the coordinating center of the Tobacco Control Legal Consortium, a national network of nonprofit legal centers providing legal technical assistance to public health professionals and advocates concerning legal issues related to tobacco and public health.1

While Executive Order 13777 requires all federal agencies to establish a regulatory reform task force and to begin examining existing regulations with the intention of “lower[ing] regulatory burdens,”2 we note that the FDAs Center for Tobacco Products (CTP) plays a vital role in protecting public health from the harms caused by tobacco products. Any attempt to roll back or repeal the few tobacco product regulations established by CTP during its short history would put public health at risk.

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1 The Tobacco Control Legal Consortium’s activities are coordinated by the Public Health Law Center, at Mitchell Hamline School of Law in St. Paul, Minnesota. The Consortium’s affiliated legal centers include: ChangeLab Solutions, Oakland, California; Legal Resource Center for Tobacco Regulation, Litigation & Advocacy, at University of Maryland Francis King Carey School of Law, Baltimore, Maryland; Public Health Advocacy Institute and the Center for Public Health and Tobacco Policy, both at Northeastern University School of Law, Boston, Massachusetts; Smoke-Free Environments Law Project, at Center for Social Gerontology, Ann Arbor, Michigan; and Tobacco Control Policy and Legal Resource Center at New Jersey GASP, Summit, New Jersey.
During the examination of CTP’s existing regulations, it is particularly important to note that, while Executive Order 13771 instructs agencies to examine only economic costs and to ignore any economic benefits when promulgating new rules – an entirely wrongheaded approach to areas like environmental, health, and safety regulation\(^3\) – Executive Order 13777 specifically requires the examination of the costs and benefits of regulation.\(^4\) The economic toll caused by tobacco products is significant and while CTP regulation may create some small economic burdens for some tobacco product manufacturers, those same regulations create tremendous economic benefits to the rest of the country.

Any efforts to roll back tobacco product regulation would result in an increase in harm to public health and that harm would have a negative impact on the national economy due to lives lost, absenteeism, and increased healthcare costs.\(^5\) If the goal of this order is truly to relieve “burdens on the American people,”\(^6\) regulations related to the product that is the single largest cause of preventable death and disease in our country should not be considered for repeal.\(^7\)

In addition, any attempts to roll back CTP regulations would require a showing that such an action meets the public health standard found throughout the Tobacco Control Act. EO 13777 does not supplant CTP’s congressional mandate to protect public health. The mere finding that a given regulation is an economic burden does not give the FDA the authority to revoke a regulation. All CTP regulatory actions must, first and foremost, protect public health, a standard that action to deregulate cannot meet given what is known about tobacco product regulation.

The remainder of this comment will focus on the arguments presented in a comment submitted December 14, 2017 by the Council of Independent Tobacco Manufacturers of America (CITMA).\(^8\) This comment casts a significant regulatory problem in a false light in an attempt to persuade the FDA to make harmful changes to its premarket review process for tobacco products. For all of the reasons discussed below, the FDA should not make those changes.

I. Tobacco products are not drug-delivery devices

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\(^{7}\) SGR 2014 at 678.

All of the specific changes requested in CITMA’s comment are centered on the idea that the review of CTP’s 905(j) Substantial Equivalence (SE) reports should be the same as the Center for Devices and Radiological Health’s (CDRH) 510(k) process. This is an absurd proposition for a variety of reasons. First, medical devices and tobacco products are entirely different categories of products and premarket review of such products ought to look entirely different as well. Medical devices are typically used by consumers to treat or mitigate diseases and medical conditions, that is, they have an important, beneficial role in society. Tobacco products do not share this characteristic.

Unlike other FDA regulated products, tobacco products have no beneficial use for consumers. In fact, half of all lifetime users of combustible tobacco products, using the products as they are intended to be used, will be killed by the products.\(^9\) And because tobacco products are addictive, most people who use them do not want to use them and yet, cannot quit.\(^10\) While many people understand that the continued use of tobacco products creates some risk, most people who smoke start during adolescence,\(^11\) a period of time when many youth underestimate the grave harm caused by smoking and overestimate their ability to quit smoking later in life.\(^12\) The confluence of these factors creates a product that has killed over 100 million people in the last century and is on pace to kill 1 billion people in the next century unless the trajectory of this epidemic is changed dramatically.\(^13\) Stringent premarket review is one tool that can contribute to this change.

Another important reason that the FDA should not make CITMA’s proposed changes to premarket review for tobacco products is that Congress did not adopt section 510(k) when drafting the Tobacco Control Act. CITMA argues that CTP should adopt CDRH’s process of merely requiring manufacturers to provide notice to the agency for some, not all, changes to products. Pointing to similarities in the language between the two statutes does not, in fact, suggest that Congress intended to mandate a similarity in the agency’s approach. Quite the opposite, differences in the statutory language are a clear indication that Congress intended the standards to operate differently. More to that point, while the Tobacco Control Act borrows some


\(^10\) SGR 2014 at 107-127.


\(^12\) Id.

language from section 510(k),\textsuperscript{14} it does not adopt the underlying structure of the device regulations. The most important difference in these two portions of the Federal Food, Drug, and Cosmetic Act is that the Tobacco Control Act does not permit the introduction of new products without an affirmative order from the agency.\textsuperscript{15} Section 510(k) existed at the time of the drafting and passage of the Tobacco Control Act and Congress could have adopted its language wholesale but it did not. Congress recognized that tobacco products are different from drug-delivery devices and adopted a more stringent premarket review process. Congress deliberately disrupted the status quo of the tobacco product market. We know this to be true because Congress stated it plainly;

\begin{quote}
The current lack of government regulation has allowed the tobacco industry to design new products or modify existing ones in ways that increase their appeal to children and that contribute to the risk and incidence of disease. Flavors and product modification not only make the products more appealing to youth, but often result in exposure to additional carcinogens and other toxic constituents. The manipulation of nicotine and other chemical levels increases addictiveness and harm.\textsuperscript{16}
\end{quote}

Congress recognized that while tobacco products are dangerous, an entirely unchecked tobacco product market was even more dangerous because of the efforts of tobacco product manufacturers to manipulate ingredients and constituents in their products to make them more addictive and many of these changes have a side-effect of making them more harmful. To solve this problem, Congress gave the FDA full authority to review all changes to tobacco products \textit{before} the products reach the market. Again, Congress made this clear;

\begin{quote}
It is essential that the Food and Drug Administration review products sold or distributed for use to reduce risks or exposures associated with tobacco products and that it be empowered to review any advertising
\end{quote}

\textsuperscript{14} Compare 21 U.S.C. § 360(k) "Each person who is required to register under this section and who proposes to begin the introduction or delivery for introduction into interstate commerce for commercial distribution of a device intended for human use shall, at least ninety days before making such introduction or delivery, report to the Secretary or person who is accredited under section 360m(a) of this title (in such form and manner as the Secretary shall by regulation prescribe)—" with 21 U.S.C. 387e(j) "Each person who is required to register under this section and who proposes to begin the introduction or delivery for introduction into interstate commerce for commercial distribution of a tobacco product intended for human use that was not commercially marketed (other than for test marketing) in the United States as of February 15, 2007, shall, at least 90 days prior to making such introduction or delivery, report to the Secretary (in such form and manner as the Secretary shall prescribe)—."


and labeling for such products. It is also essential that manufacturers, prior to marketing such products, be required to demonstrate that such products will meet a series of rigorous criteria, and will benefit the health of the population as a whole, taking into account both users of tobacco products and persons who do not currently use tobacco products.17

Congress could have adopted section 510(k)’s process of notification prior to marketing for some changes to tobacco products. Instead, it deliberately chose a more stringent process for tobacco products and it did so with good reason that it explicitly laid out in the Act.

The FDA must continue to require an affirmative marketing order prior to the introduction of new tobacco products for all of the reasons that Congress made plain in the Act. The agency can and should adopt regulations and guidance to clarify what is required to satisfy the statutory standards established for each pathway to the market. However, the FDA has not been granted the authority to defer product review until after a product has been introduced to the market. The structure of the Tobacco Control Act simply does not allow CTP to adopt a process similar to CDRH’s notification process.

II. CTP’s premarket review process is not overly burdensome and its burden of proof is not impossible.

The vast majority of CITMA’s comment focuses on what it characterizes as the “overly burdensome” premarket review process. The comment provides a handful of examples that are alleged to provide evidence for that conclusion. However, almost every example in the comment is related to the Provisional SE review process. This is problematic because Provisional SE reports represent products that are currently being marketed without affirmative authorization. These products are some of the only tobacco products that have been allowed to enter the market without an affirmative order from the agency and the only class of products granted a specific exemption under the Tobacco Control Act to enter the market without review. Because these products are already on the market, CITMA’s argument that the slow review of these products creates a burden for the regulated industry fails entirely. In fact, the opposite is true. CTP’s slow review of Provisional SE reports is putting public health at risk. Attached to this comment is a copy of an article outlining some of the most important problems with CTP’s review process to date, highlighting the lack of action on most Provisional SE reports.18 The slow review of

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Provisional SE reports is indeed problematic but is the CTP premarket review process where there is the least burden on the regulated industry. CITMA’s examples that relate to the review of Provisional SE reports provide no evidence to support its conclusions that the premarket review process is overly burdensome. To better uphold the public health standard in all its activities, the FDA should reject industry pressure to relax the premarket review process and instead adopt the suggestions from the attached article.

CITMA also rails against what it views as CTP’s “impossible burdens of proof.” The comment fails provide any evidence supporting its dire claim that tobacco product manufacturers cannot meet the evidentiary standards established by CTP. CITMA highlights CTP’s Not Substantially Equivalent (NSE) determination for Pall Mall Deep Set Recessed Filter Menthol cigarettes as an example of the problem. CITMA’s characterization of this determination is plainly wrong. In fact, this review is an example of the industry’s attempts and failures to manipulate the review process, not evidence of the imposition of an impossible standard. CTP’s Technical Project Lead (TPL) Memo indicates that for Pall Mall Deep Set Recessed Filter Menthol and three other varieties of cigarettes, R.J. Reynolds (RJR) identified the predicate product as “all cigarettes commercially marketed in the United States as of February 15, 2007.” The Tobacco Control Act is clear that the SE process is a scientific review of two particular products, not one product and an amalgam of products. FDA guidance available at the time these reports were submitted also confirms that this is the process. RJR undoubtedly knew that it was supposed to select a single predicate product for each of its SE reports and it chose not to. The NSE determination was the appropriate disposition of a deficient application, not indicative of any problem with the premarket review process.

While CITMA highlights CTP’s discussion of the reports’ deficiencies with respect to “sweeteners and other non-characterizing flavoring ingredients” noting that “FDA summarily dismissed these data,” the reality is that the data was not related to the predicate product. Instead, the data compared the new product to “all other marketed cigarettes.” The conclusion again is not that the FDA dismissed relevant data but that the agency properly determined the product was NSE after carefully considering the deficient application.

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It is perplexing to hold up these four SE reports as evidence of the FDA’s “impossible burden of proof” as RJR was given numerous attempts to correct the many deficiencies. In fact, the FDA contacted RJR at least seven times to identify deficiencies and RJR sent several unsolicited amendments as well, seven amendments total for each of the four reports. Even after amendments, the SE reports remained deficient in multiple ways. The TPL memo identifies twenty-six total deficiencies across the four reports, while only one is necessary to support a rejection of a report. There were deficiencies in each area of the FDA’s different scientific reviews: chemistry, engineering, toxicology, social science, and addiction. In addition, CTP has issued hundreds of SE orders to dozens of companies, far more than the denials it has issued, a strong indication that the burden of proof is not too high.

Finally, one other point from this section of CITMA’s comment bears discussion. CITMA claims that CTP has not published any information or guidance regarding how a manufacturer might demonstrate that a new product with different flavoring ingredients from its predicate are substantially equivalent and that in practice this “appears to be impossible.” CITMA again offers an example that seems to support the opposite of its own conclusion. CTP issued an NSE order for Maverick Menthol Silver Box 100s, which identified as its predicate Kent III Ultra Lights 100s, a non-menthol cigarette.22 Given all that is known about menthol in cigarettes,23 it is clear that the addition of menthol to a non-menthol cigarette raises different questions of public health.24 The fact remains that the FDA and the Tobacco Products Scientific Advisory Committee have independently reviewed the available scientific evidence and concluded that the removal of menthol cigarettes from the marketplace would benefit public health.25 Given that conclusion, it stands to reason that the inverse is

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equally true: the addition of menthol cigarettes to the marketplace is harmful to public health. Therefore, a menthol cigarette can never be found to be substantially equivalent to a non-menthol cigarette; this one change to the cigarette has significant and detrimental effects on public health. CITMA’s comment states that the applicant was not given an opportunity to respond to this conclusion which seems unlikely as this particular SE report was amended several times.26

There is also significant evidence that the addition of flavors other than menthol to cigarettes without those flavors raises different questions of public health. Flavor additives in cigarettes affect palatability and appeal which in turn affects rates of youth experimentation. Increased rates of youth experimentation lead to increased rates of addiction which lead to increased rates of disease. The fact remains that all tobacco products are harmful and cigarettes in particular, which seems to be the focus of CITMA’s comment, are incredibly deadly. For all of the reasons discussed at length in the first section of this comment, Congress deliberately created a high bar to market new tobacco products. CITMA’s claim that the premarket review process makes it impossible to receive marketing orders for new products is plainly untrue.

III. Conclusion

The rollback of any of the regulations promulgated by CTP could have disastrous consequences to public health. Any such deregulation would create much greater economic burdens than it would relieve. It is also not within the FDA’s statutory authority to revoke tobacco product regulations solely because of economic conclusions.

In addition, CTP should not and cannot adjust the premarket review process to make it operate more like CDRH’s 510(k) process. In order to strengthen the public health benefits of premarket review, CTP should adopt the changes discussed in FDA’s Mispaced Priorities: Premarket Review Under the Family Smoking Prevention and Tobacco Control Act.


26 The list of amendments for this report is redacted and the exemption to the Freedom of Information Act that is invoked is (b)(4), for information that is trade secret or confidential commercial or financial information. Similar information is not redacted in other TPL memos and the format of this and other TPL memos indicates that the redacted information is the tracking number of the amendments. This information is neither trade secret, nor confidential commercial or financial information and thus is not properly redacted under FOIA.
Respectfully,

Joelle Lester  
Director

Desmond Jenson  
Senior Staff Attorney

Attachments
FDA’s misplaced priorities: premarket review under the Family Smoking Prevention and Tobacco Control Act

Desmond Jenson,1 Joelle Lester,1 Micah L Berman2

ABSTRACT
Among other key objectives, the 2009 Family Smoking Prevention and Tobacco Control Act was designed to end an era of constant product manipulation by the tobacco industry that had led to more addictive and attractive products. The law requires new tobacco products to undergo premarket review by the US Food and Drug Administration (FDA) before they can be sold. To assess FDA’s implementation of its premarket review authorities, we reviewed FDA actions on new product applications, publicly available data on industry applications to market new products, and related FDA guidance documents and public statements. We conclude that FDA has not implemented the premarket review process in a manner that prioritises the protection of public health. In particular, FDA has (1) prioritised the review of premarket applications that allow for the introduction of new tobacco products over the review of potentially non-compliant products that are already on the market; (2) misallocated resources by accommodating the industry’s repeated submissions of deficient premarket applications and (3) weakened the premarket review process by allowing the tobacco industry to market new and modified products that have not completed the required review process.

In 2009, the US Congress passed the Family Smoking Prevention and Tobacco Control Act (Tobacco Control Act), providing the US Food and Drug Administration (FDA) with the authority to regulate tobacco products. As part of that authority, Congress provided that no new regulated tobacco products could enter the market without first undergoing review by FDA. In a compromise negotiated with the tobacco industry, the law ‘grandfathers’ tobacco products that were already on the market.1 Products that were commercially available at the time the law was introduced, and have not been changed in any meaningful way, do not require FDA authorisation to stay on the market. However, the law mandates that a manufacturer submit to FDA review before any new product, including new versions of previously available products, can be sold at retail.2 One aim of the requirement is to address the tobacco industry’s history of manipulating its products to maximise addictiveness and increase attractiveness to consumers, and to prevent more harmful products from ever entering the market.1-8

In the almost 7 years since the enactment of the Tobacco Control Act, FDA has failed to implement the premarket review process in a manner that maximises the protection of public health. Instead, as explained in this Special Communication, the agency has misplaced its priorities, and thereby has undermined the potential public health benefits of tobacco regulation, in three distinct ways. First, rather than prioritise the removal of non-compliant products from the marketplace, FDA has given precedence to the review of applications that allow for the introduction of new tobacco products. Second, FDA has accommodated the tobacco industry’s repeated submission of deficient premarket applications, rather than dismissing such flawed applications outright or allowing only reasonable amendments. Finally, even though industry marketing activities are widely publicised, FDA has failed to prioritise the enforcement of premarket review against companies that have avoided the process entirely and introduced new or modified products to the market without authorisation. These conclusions are based on our review of FDA actions on new product applications, publicly available data on industry applications to market new products, and the agency’s guidance documents and public statements.

BACKGROUND ON THE TOBACCO CONTROL ACT’S PREMARKET REVIEW PROVISIONS
The cut-off date for products that are grandfathemed and do not require FDA review is 15 February 2007.1 Any new or modified product introduced after that date must be authorised by FDA before it can be sold. This includes any entirely new brand or sub-brand of a product, as well as any modification to a legally marketed product.1 Whether FDA will authorise a new product to be sold depends on the manufacturer’s ability to demonstrate that it has satisfied the criteria for one of the regulatory pathways for new products (figure 1). Under the Premarket Tobacco Product Application (PMTA) pathway, the manufacturer must show that introduction of a new product would be ‘appropriate for the protection of the public health’, taking into account ‘the risks and benefits to the population as a whole, including users and nonusers of the tobacco product’.9 In essence, this requires the applicant to show that, on balance, the sale of the new product would likely reduce tobacco-related harms. The Substantial Equivalence (SE) pathway provides for less rigorous review if a manufacturer can show that its product is nearly the same as a predicate grandfathered product. When this pathway is being used, FDA’s task is to determine whether the product is different from the predicate in any way that raises ‘different questions of public health’.10 If so, the SE pathway is
not available, and the product must go through PMTA review before it can be sold. By contrast, if the new product does not raise any ‘different question of public health’, FDA will issue an SE order permitting that product to be marketed.

Although the general rule is that premarket review is required for both the PMTA and SE pathways, the Tobacco Control Act created an exception for SE applications (also termed ‘SE Reports’ by FDA) submitted by 22 March 2011. These products with SE applications submitted by that date are permitted to be sold while their applications are under review. FDA calls these applications ‘Provisional’ SE applications, because the products are provisionally on the market. The industry is free to manufacture and sell these products, but if FDA later determines that such a product is not substantially equivalent to a predicate product, it must be removed from the market.

While FDA’s SE review process mimics the agency’s SE review of modified medical devices, the administration of that authority ought to look very different in the tobacco context. On the medical device side, FDA’s mission overlaps significantly with the regulated industry’s goal: to facilitate the provision of safe and effective devices to consumers. It is in the public’s interest to get modified medical devices to market as quickly as possible (so long as they are safe and effective), and it is in a device maker’s best interest to collaborate with FDA to ensure that its devices have minimal to no unintended consequences. The bad publicity and potential legal liability that comes from a device that causes more harm than good can be exceptionally damaging to a device maker.

By contrast, the SE review process for tobacco products is not designed to ensure that modified products are safe; it is instead intended to ensure that any changes to tobacco products do not create additional public health harms. However, because tobacco products are already so harmful, the tobacco industry has little incentive to ensure that this review is effective. The industry will not be penalised by the marketplace for selling products that are marginally more harmful, and because its products are addictive, the industry’s only incentive is to maximise product availability, addictiveness and appeal, and thereby increase sales. Furthermore, unlike in the medical device context, there is no public benefit to rushing new tobacco products to market. Public health gains are likely to accrue only if the SE requirements are rigorously applied and the industry is forced to go through the more rigorous PMTA process when appropriate. Thus, FDA and the tobacco industry do not share a common set of interests; FDA’s goal should be to ensure that the SE requirements are scrupulously enforced, while the industry has every incentive to evade those same requirements. Yet, FDA’s implementation of the SE review process for tobacco has reflected priorities that are more suitable for the review of devices, where it is an appropriate goal to move new or modified products to the market as quickly as possible. These misplaced priorities are having a significant negative impact on public health.

**MISPLACED PRIORITY #1: FDA PRIORITISES THE INTRODUCTION OF NEW TOBACCO PRODUCTS OVER THE REMOVAL OF NON-COMPLIANT ONES**

The tobacco industry submitted 3517 Provisional SE applications, nearly all of them in the final few weeks before the 22 March 2011 deadline. This avalanche of applications dwarfs the number of submissions to all other new product pathways in the 5 years since that deadline, including ‘Regular’ SE applications (those submitted after 22 March 2011) (figure 2). FDA has focused its review on Regular SE applications rather than Provisional SE applications. This prioritisation has important implications for public health because allowing new products onto the market through the Regular SE pathway will have no beneficial impact on public health. However, the removal of Provisional SE products from the market could secure public health gains, as any non-compliant products would be found to have raised different questions of public health, and thus, have the potential to pose new harms to public health. Prioritising Regular SE applications serves the tobacco industry’s interest in getting new products to the market as quickly as possible, and further delays agency action on those products that are already

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**Table: Premarket review pathways. FDA, US Food and Drug Administration; SE, Substantial Equivalence; PMTA, Premarket Tobacco Product Application.**

<table>
<thead>
<tr>
<th>Path 1: Regular Substantial Equivalence (Regular SE)</th>
<th>Path 2a: Provisional Substantial Equivalence (Provisional SE)</th>
<th>Path 2b: Provisional Substantial Equivalence (Provisional SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Application contains:</td>
<td>Analysis of the similarities and differences of: 1. a product that was introduced to the market between 2/15/2007 and 3/22/2011, AND 2. a predicate product</td>
<td>Analysis of the similarities and differences of: 1. a product that has never been previously marketed, AND 2. a predicate product</td>
</tr>
<tr>
<td>Eligible Predicate Products:</td>
<td>A product that was marketed on 2/15/2007</td>
<td>A product that was marketed on 2/15/2007, or a product authorized through the SE pathway (Provisional or Regular)</td>
</tr>
<tr>
<td>Product can be authorized if:</td>
<td>Manufacturer demonstrates that: 1. the new product has the same characteristics as its predicate, OR 2. any differences in the characteristics of the new and predicate products do not raise different questions of public health</td>
<td>Manufacturer demonstrates that: 1. the new product has the same characteristics as its predicate, OR 2. any differences in the characteristics of the new and predicate products do not raise different questions of public health</td>
</tr>
<tr>
<td>Marketing status:</td>
<td>Cannot be sold until authorized by the FDA</td>
<td>Allowed to be sold until removed by the FDA</td>
</tr>
</tbody>
</table>

*Manufacturers can also seek an exemption from substantial review if the differences between the new product and predicate product are very minor.  
†Products authorized through the SE pathway are also eligible predicate products for this pathway. However, because no SE authorizations were issued before 3/22/2011, when the Provisional SE applications were due, all applications necessarily used products that were marketed on 2/15/2007 as their predicates.*
on the market. Given FDA's mandate to protect public health in its regulation of tobacco products, FDA should prioritise the review of Provisional SE applications instead.

FDA's prioritisation of Regular SE applications over Provisional SE applications can be confirmed by examining FDA's public data regarding the status of its reviews. The multi-step SE review process concludes with a scientific review, analysing the differential characteristics of the new and predicate products. The number of applications reaching this final stage provides a clear picture of FDA's priorities. Of the 3517 Provisional SE applications that have been submitted, FDA has only initiated scientific review of 645 of them, about 18%. By contrast, it has initiated scientific review of 1904 of the 1917 Regular SE applications that it has received, more than 99%. Moreover, of the 645 Provisional SE applications that are currently under review, FDA initiated the review of the vast majority (604) in 2014 or 2015. While this progress is a positive development, all these applications were submitted in March 2011. For Regular SE applications, scientific review on the first applications began in May 2012, and the agency has steadily initiated review of new applications since then.

FDA also has publicly confirmed that it is prioritising Regular SE applications, explaining that this focus is driven by the fact that Regular SE applications represent products that are not currently on the market. There is no public health justification for trying to move new products to the market as quickly as possible. There is no statutory deadline by which FDA must review Regular SE applications, and focusing on the introduction of new products rather than the removal of non-compliant ones is inconsistent with the goals of the Act, and does not protect public health.

The pace of FDA review further exacerbates this problem. If the agency were acting quickly on Regular SE applications, it could eventually clear the backlog of Provisional SE applications, despite not prioritising them. Although the FDA has taken action to speed up its review, steady action on Regular SE applications and action on a handful of Provisional SE applications has not yet significantly reduced the backlog, with the number of SE applications pending before the agency having remained above 3,500 since March 2011 (figure 3). FDA has established performance measures for its review of Regular SE applications and plans to reach a point whereby it would begin its review of all new SE applications as soon as they were submitted. Notably, however, the agency has not established any performance measures for its review of Provisional SE applications, claiming that it lacks sufficient experience with them. This justification is non-sensical because the only differences between Provisional and Regular SE applications are (1) the date that the agency received them and (2) the fact that Provisional SE products are already on the market. Because of the agency’s slow pace of review and focus on Regular SE, rather than Provisional SE applications, FDA has permitted unauthorised products to remain on the market. Indeed, for more than 5 years, as many as 3000 tobacco products have been in stores, gaining a foothold in the market, without any determination by FDA that they have met the proper legal standards.

Reviewing Provisional SE applications might not need to be a top priority if the tobacco industry could be trusted to submit applications only for products that were, in fact, nearly identical to the grandfathered predicate products. Given the tobacco industry’s history of deception, however, this is not an assumption that can safely be made. Moreover, the substantial number of SE submissions received by FDA immediately before the March 2011 deadline suggests that instead of making a good-faith effort to determine which products were ‘substantially equivalent’ to grandfathered products, the tobacco industry instead sought to keep as many products on the market as possible, regardless of a product’s eligibility for the SE pathway. Indeed, until September 2015, every final FDA decision on a Provisional SE application had found that the product at issue was not substantially equivalent (NSE) to the predicate product, as the application had claimed (figure 3). In September 2015, FDA did grant SE orders to 98 products that had undergone a new streamlined review process for Provisional SE applications with only labelling or packaging changes. However, the remaining backlog of more than 3000 Provisional SE applications should prompt alarm that there are likely more Provisional SE products still on the market that do not meet the statutory requirements. Use of these potentially non-compliant products is likely increasing overall health harms from tobacco use.

MISPLACED PRIORITY #2: FDA IS SQUANDERING RESOURCES BY REPEATEDLY ACCOMMODATING THE INDUSTRY’S SUBMISSION OF DEFICIENT PREMARKET APPLICATIONS

It is unclear to what extent the slow pace of FDA's review of SE applications is due, in part, to unnecessary and unwarranted accommodation of the tobacco industry. Under the Tobacco Control Act, it is the applicant’s responsibility to demonstrate compliance with the prerequisites for a marketing order under either PMTA or SE pathway. Although FDA can and should assist applicants with understanding the requirements of the Tobacco Control Act, FDA has squandered resources and further delayed the removal of illegitimate tobacco products from the market by making numerous accommodations to tobacco companies that submitted clearly deficient premarket applications.

This excessive level of accommodation is illustrated by the agency’s first action on Provisional SE applications, which was taken in February 2014. The four applications at issue, submitted in 2013, were for ‘flavoured’ SE products — electronic cigarettes and related services. This FDA policy change and the tobacco industry’s current legal challenge to the policy are not discussed in this paper. The public health implications of this important and potentially harmful policy warrant significant discussion by the public health community but, due to space limitations, this paper will not address this subject.
submitted by the same manufacturer, failed to identify a predicate product to serve as the comparison for the new products. The failure to identify a predicate product should represent a fatal deficiency in an SE application. However, FDA did not contact the manufacturer to request the identification of the missing predicate products until 19 March 2013, roughly 2 years after the applications were submitted. The agency had eight unsuccessful follow-up communications, with the applicant unable to adequately identify the predicate. FDA finally issued NSE orders on 20 February 2014, removing the products from the market almost 3 years after the agency received the applications.

FDAs extended dialogue regarding a fatally deficient application reveals an important issue. At least some of the manufacturers submitting SE applications either have a significant misunderstanding of the most basic requirements of the process, or they are deliberately attempting to exploit the process. While it is possible that manufacturers did not understand the SE process by the provisional deadline, that is unlikely given the clear guidance provided by FDA regarding what must be included in an SE application. It seems more probable that some manufacturers acted in bad faith and knowingly submitted deficient applications. It would be reasonable for the agency to allow an amendment or two to the scientific information included in an application. But as the agency’s information shows, many of the deficiencies focus on the mere identity of the predicate or new product, which ought not be pieces of information that require multiple follow-ups, let alone eight or more, as has often been the case. In any event, whether the manufacturer was ill-informed or flouting the law, it is FDA’s responsibility to quickly reject fatally flawed applications and remove non-compliant products from the market.

It is unclear how many other fatally deficient Provisional SE applications are pending before FDA. According to the agency, there have been significant deficiencies in nearly all the SE applications it has reviewed. The agency’s Provisional NSE orders show the scope of these deficiencies (figure 4). For example, FDA orders rejecting 10 Provisional SE applications in May 2015 revealed that neither the new products nor the predicate products were uniquely identified despite at least five attempts to contact the manufacturer. In August and September 2015, NSE orders were issued for additional Provisional SE products that did not adequately identify the predicate or new products. The August NSE orders were issued to a manufacturer who did not respond to the agency’s 16 attempted contacts over the course of 2 years. The September NSE orders were issued to a manufacturer who had notified the agency several years prior that the company had gone out of business. Even after receiving this notification, the agency continued to request either supplementary information or a formal withdrawal 10 times over a period of more than 2 years. In another case, rather than selecting an individual predicate product for its SE applications, as is required by the Tobacco Control Act, RJ Reynolds (RJR) submitted SE applications identifying ‘a composite of all cigarettes commercially marketed in the United States as of 15 February 2007’. Eventually, the agency instructed the manufacturer to amend its SE applications more than 2 years after they were submitted. When such predicate products were finally identified (after multiple requests from FDA), they clearly differed in meaningful ways from the new products. One new product contained a crushable menthol capsule not found in the predicate product. There is no reason why FDA could not have taken FDA years to act on these applications. RJRs decision to use the Provisional SE pathway was dubious, given the obvious weakness of its argument for SE. But because it took so long for FDA to act, this gambit enabled these products to stay on the market for more than 4 years.

In each of these cases, there was a significant delay between the submission of a Provisional SE application and the first contact between the agency and the applicant (figure 4). This delay is a direct result of the agency’s prioritisation, not a result of a lack of agency resources. This is evidenced by the significantly shorter delay in contacting Regular SE applicants, and the fact that even though the Provisional SE applications were received first, Regular SE applicants were contacted 11 months earlier. The first Provisional SE applications were submitted to the agency in November 2010, but the first requests for additional information were sent to manufacturers in December.


2012, a 25-month delay. For Regular SE applications, the first submissions were received in late March 2011, but the first requests for additional information were sent in January 2012, only a 10-month delay. The interconnectedness of the agency’s priority of review, and its slow pace of action is important. Together, they have prevented the agency from making any appreciable progress in clearing its massive backlog of Provisional SE applications.

FDAs overly generous approach to clearly deficient applications further delays an already slow review process. More problematically, it establishes a culture in which there is seemingly no expectation that tobacco product manufacturers comply with the statutory requirements, or FDAs guidance. If an application is found to be deficient—even in fundamental ways—FDA will provide the manufacturer with repeated opportunities to modify the application. With the development of a new regulatory scheme, it is not unreasonable for the agency to provide initial feedback and request supplementary information on industry applications. However, it is not FDAs responsibility to do the industry’s work. Because the agency is devoting significant resources to accommodating egregiously—and perhaps deliberately—deficient applications, it is more difficult for FDA to pursue other regulatory actions that might significantly impact public health.

MISPLACED PRIORITY #3: FDA INACTION IS UNDERMINING THE PREMARKET REVIEW PROCESS BY ALLOWING THE INDUSTRY TO MARKET NEW, UNAUTHORISED PRODUCTS

Even though FDAs slow review of Provisional SE applications has allowed the tobacco industry to continue marketing products that were available before 22 March 2011, manufacturers have been eager to introduce new products after that date. Some companies have even introduced brand new products to the market, or significantly modified existing products, without any authorisation from FDA, in clear violation of the Tobacco Control Act. Yet, FDA has, thus far, failed to take any public enforcement action against these companies.

For example, Philip Morris, USA, launched Marlboro Black and Marlboro Black Menthol in December 2011. This version, the company also began marketing Marlboro NXT in 27 states in September 2012, and expanded the marketing to the remaining 23 states in July 2013. Similarly, RJR introduced a new brand of heat-not-burn cigarettes, called Revo, in February 2015, and also introduced two new conventional cigarettes, Camel White and Camel White Menthol, in April 2015. Public statements by the tobacco companies leave no doubt that these products are ‘new products’ that ought to be subject to premarket review. There is also no doubt that FDA has not issued orders authorising the marketing of these products, and most of them are still available in retail stores. RJR discontinued Revo because the product did not meet the company’s expectations, and the manufacturer has also removed Camel White from the market without a public announcement, but the other products remain available.

In addition to these widely publicised new product releases, smokeless tobacco product manufacturers are making significant modifications to their products, the types of modifications that must be cleared with FDA prior to marketing. For example, between 2010 and 2011, Marlboro Snus introduced a larger ‘round tin’, similar in appearance to conventional moist snuff. The snus pouches in the ‘round tin’ packaging are larger and contain a higher moisture content than the previous version. These changes appear to play a significant role in the level of nicotine and tobacco-specific N-nitrosamines in these products, and therefore have substantial implications for public health. Because FDA does not make such information available, it is not clear whether Altria (parent company of Philip Morris, USA) submitted Provisional SE applications for Marlboro Snus products by the 2011 deadline. If so, these SE applications would have been inappropriate, as these products were clearly modified after 15 February 2007, and any changes after that date that ‘raise different questions of public health’ require a PMTA application, not an SE application. As FDA has yet to act on any SE applications for Marlboro Snus products, it is therefore the case that either (1) Altria is abusing the SE

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Number of Contacts Initiated by FDA</th>
<th>Days on Market with Known Deficiency</th>
<th>Date of First Contact</th>
<th>Date of NSE Order</th>
<th>Nature of Deficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Star Scientific, Inc.</td>
<td>4</td>
<td>665</td>
<td>11/01/2012</td>
<td>06/28/2014</td>
<td>No side-by-side quantitative comparison of “other features”</td>
</tr>
<tr>
<td>Eagle River Importers, Inc.</td>
<td>5</td>
<td>744</td>
<td>05/06/2013</td>
<td>05/20/2015</td>
<td>New and predicate products not uniquely identified</td>
</tr>
<tr>
<td>R.J. Reynolds Tobacco Company</td>
<td>7</td>
<td>900</td>
<td>03/29/2013</td>
<td>09/15/2015</td>
<td>Deficient predicate product information</td>
</tr>
<tr>
<td>Jash International, Inc.</td>
<td>8</td>
<td>339</td>
<td>03/19/2013</td>
<td>02/21/2014</td>
<td>New and predicate products not uniquely identified</td>
</tr>
<tr>
<td>Pacific Standard Manufacturing Corporation</td>
<td>10</td>
<td>1024</td>
<td>11/14/2012</td>
<td>09/04/2015</td>
<td>New and predicate products not uniquely identified</td>
</tr>
<tr>
<td>LIT Distributor, Inc.</td>
<td>12</td>
<td>923</td>
<td>04/04/2013</td>
<td>10/14/2015</td>
<td>New and predicate products not uniquely identified</td>
</tr>
<tr>
<td>California Clinical Supply Company</td>
<td>16</td>
<td>959</td>
<td>12/20/2012</td>
<td>08/06/2015</td>
<td>New and predicate products not uniquely identified</td>
</tr>
</tbody>
</table>

Figure 4 FDA response to Provisional SE report deficiencies. FDA, US Food and Drug Administration; SE, Substantial Equivalence.
process, aided by FDA’s failure to review Provisional SE applications in a timely manner, or (2) Altria is making significant product modifications without the required FDA review, and FDA has failed to enforce the law in a timely way.

Although the agency ought to be able to, FDA is not identifying new products entering the market without marketing orders. One readily apparent solution to this problem is for the agency to implement its authority to require a track-and-trace programme for tobacco products. Such a system, where each individual tobacco product has a unique identification code or computer chip that allows the agency to track the product from the assembly line to a consumer’s hands, is contemplated by the Tobacco Control Act, and public health groups have asked FDA to implement this authority. A thorough track-and-trace system would give FDA a robust regulatory tool to prevent unauthorised products from entering the market.

It is equally important for the agency to monitor significant changes to existing products, particularly when these changes result in increases to addictive and carcinogenic constituents. Requiring premarket review of new tobacco products is a basic pillar of the Tobacco Control Act’s regulatory structure. If FDA permits companies—including the major cigarette manufacturers—to modify their products without completing the required premarket review process, why would any company comply with the law? The lack of quick and aggressive FDA action against companies that are brazenly introducing new products and modifying existing ones undermines the premarket review process and fails to protect public health.

POLICY RECOMMENDATIONS AND CONCLUSION

FDA has significant opportunities to improve the premarket review process to better protect public health. The authors suggest the following steps for immediate, impactful changes:

1. FDA should reverse its prioritisation of Regular over Provisional SE applications. Provisional SE products that are currently on the market have been given a free pass for more than 5 years, despite the fact that many of them likely do not meet the legal test for SE.

2. FDA should immediately identify Provisional SE applications that have failed to identify either the new or predicate product. Such applications that have not already been corrected should be given only one attempt to correct the deficiency before the agency issues an NSE order, creating a greater incentive for the industry to submit complete applications.

3. FDA should establish benchmarks for the length of time a deficient application may remain pending, and the number of times FDA will contact an applicant to seek additional information. When scientific information cannot be corrected within 90 days, or the applicant fails to respond to requests for additional information, the agency should promptly issue an NSE order rather than making additional attempts to solicit amendments. The agency must no longer tolerate gross deficiencies; the tobacco industry has had years to correct deficient pending applications, and there has been ample information released regarding the types of deficiencies that result in NSE orders. This is true even for applicants who have not been contacted regarding deficiencies. The statute requires FDA to act based on information provided by the applicant, and if that information is deficient, FDA is required to reject an application. Therefore, it is the applicant’s responsibility, not FDA’s, to ensure that an application is complete and accurate.

4. FDA should begin monitoring the tobacco product market more closely. In order to do so, the agency should implement a robust track-and-trace system. FDA should also begin regularly reviewing tobacco industry public announcements and biannual manufacturer registrations with the agency so that it can quickly identify and take enforcement action to remove any products that enter the market without authorisation.

5. To increase the participation of the public health community, FDA should make its premarket review activities more transparent, and provide educational materials designed for the public health community. For all NSE orders, FDA should publish the full applications with minimal redactions (only those required by law). FDA should also publish the product names from all Provisional SE applications that have been submitted. Similarly, FDA should identify any products that have been certified as grandfathered tobacco products. Providing this information will allow the public health community to supplement the agency’s monitoring of the tobacco product marketplace and identify products entering the market without authorisation.

FDA’s premarket review authority rests on the premise that without the express authorisation of the agency, no new tobacco product can enter the marketplace. Unless FDA truly controls entry to the tobacco product market, as the Tobacco Control Act clearly requires, the public health gains of a review process will be minimal. The agency has had nearly 7 years to implement a regulatory system, yet is has failed to meet this basic prerequisite for effective regulation. Instead, FDA has set priorities that undermine its ability to protect the public.

Rather than prioritising the review of Provisional SE products that have been allowed to remain on the market without any oversight, FDA has facilitated the introduction of additional tobacco products. Likewise, rather than guard the marketplace from illegal or otherwise unauthorised products, FDA has wasted resources by giving significant leeway to tobacco companies to correct applications that are grossly incomplete if not deliberately deficient. Significant reform is needed for FDA to satisfy its obligation to protect public health.

What this paper adds

- While the Tobacco Control Act has ushered in an era of premarket review of new tobacco products, the US Food and Drug Administration’s (FDA) implementation and enforcement of the premarket review requirements has not fulfilled the agency’s obligation to protect public health.
- FDA’s decision to prioritise the review of Regular Substantial Equivalence (SE) applications over Provisional SE applications has allowed the industry to keep thousands of unreviewed provisional products on the retail market.
- FDA is providing excessive opportunities to the tobacco industry to correct deficient submissions, leading to significant delays in removing unreviewed provisional products from the retail market.
- Despite the premarket review requirements, there is evidence that the tobacco industry is introducing new products that have not been authorised by FDA, and the agency has yet to take an action to stop or prevent this practice despite the fact that the industry’s actions have been made public.

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