Lorillard, Inc.

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VIA ELECTRONIC SUBMISSION

Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

Re: Draft Guidance for Industry: Applications for Premarket Review of New Tobacco Products (Docket No. FDA-2011-D-0212)

Dear Sir or Madam:

Lorillard Tobacco Company (Lorillard) submits these comments in response to Food and Drug Administration's (FDA) Draft Guidance for Industry: Applications for Premarket Review of New Tobacco Products (the Guidance) issued on September 28, 2011.[1] At this time, Lorillard manufactures and sells cigarettes in the domestic market. Lorillard's comments with respect to the Guidance are limited to premarket tobacco product applications (PMTAs) for cigarettes.

While Lorillard appreciates that the FDA issues guidance to aid persons submitting PMTAs under section 910 of the Federal Food, Drug, and Cosmetic Act (FDCA), the Guidance does not provide clear assistance to Lorillard with respect to the requirements of section 910.

First, the Guidance identifies requirements that will either be impossible or unreasonably burdensome to fulfill and that, thereby, *de facto* prohibit the introduction of new cigarette products. The plain language of the Family Smoking Prevention and Tobacco Control Act (the Act)[2] does not support an approach by FDA that would essentially freeze the cigarette market as of February 15, 2007[3], other than new cigarette products that are substantially equivalent under Section 905(j) (or exempt from the SE requirements) of the Act[4] or cigarettes that meet the requirements of a MRTP under section 911 of the Act.[5] Unreasonably burdensome and

[1] 76 Fed. Reg. 188 (Sept. 28, 2011).
[2] Pub. L. No. 111-31, 123 Stat. 1776 (2009).
[3] Act, Section 907(d)(3).
[4] Lorillard incorporates by reference its comments dated February 4, 2011 to Guidance for Industry and FDA Staff: Section 905(j) Report: Demonstrating Substantial Equivalence for Tobacco Products (Docket No. FDA-2010-D-0635; and its comments dated March 22, 2011 to Proposed Rule: Tobacco Products, Exemptions From Substantial Equivalence Requirements (Docket No. FDA-2010-N-0646).
[5] Lorillard incorporates by reference its comments dated September 23, 2011 to Scientific Evaluation of Modified Risk Tobacco Product Applications (Docket No. FDA-2011-N-0043).

unnecessary requirements for approval of new cigarette PMTAs will stifle competition in the cigarette market.

Second, cigarettes and other tobacco products, by their nature, must have different regulatory requirements than those applied to drugs, medical devices and other products regulated by the FDA. Cigarettes are essentially an agricultural product and, as such, the inherent variabilities of the product must be taken into account. Cigarettes cannot be designed or manufactured to the strict tolerances possible with respect to other products regulated by FDA such as drugs and medical devices. In addition, the risks that accompany smoking cigarettes currently and legally on the market must be considered when FDA reviews PMTAs for new cigarette products.

Third, the Guidance does not provide sufficient clarity with respect to the required contents of a PMTA. The Guidance does not clearly distinguish how the requirements for the submission of a PMTA under section 910 differ from the requirements for the submission of an application for a modified risk tobacco product (MRTP) under section 911 of the Act.

FDA should revise the Guidance to provide greater clarity, to eliminate unnecessary and unreasonable burdens on FDA and tobacco product manufacturers, and to conform to Congressional intent reflected in the plain language of the Act.

Lorillard offers the following comments on the Guidance.

I. Any PMTA must demonstrate that it is "appropriate for the protection of the public health"

The Guidance sets forth the requirements of the Act:

> *Section 910(b)(1)(A) of the FD&C Act requires that a PMTA contain "full reports of all information, published or known to, or which should reasonably be known to, the applicant, concerning investigations which have been made to show the health risks of such tobacco product and whether such tobacco product presents less risk than other tobacco products."*

and

> *The information provided in the application described in section V.A of this guidance should present data and information sufficient to enable FDA to make a finding that the marketing of a new tobacco product is "appropriate for the protection of the public health" (section 910(c)(4) of the FD&C Act). The statute provides that the basis for this finding shall be determined:*
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> > *with respect to the risks and benefits to the population as a whole, including users and nonusers of the tobacco product, and taking into account —*
> >
> > *(A) the increased or decreased likelihood that existing users of tobacco products will stop using such products; and*
> >
> > *(B) the increased or decreased likelihood that those who do not use tobacco products will start using such products.*

The Guidance requires that applicants provide evidence regarding whether a new tobacco product will pose increased risks to the individual smoker. In addition, the Guidance requires the provision of evidence regarding whether the product will increase the uptake of smoking or decrease cessation among the population as a whole. FDA should not interpret the statutory language in a manner that makes it impossible or unreasonably burdensome for a tobacco product manufacturer to satisfy these requirements. The requirement showing that a new cigarette product is "appropriate for the public health" should not be as burdensome as that required for a MRTP cigarette product, because no reduced risk or exposure claims will be allowed for any new cigarette product which does not qualify as a MRTP.[6]

The health risks attending tobacco product use, generally, and cigarette smoking, specifically, are numerous and well-documented. There is a general scientific consensus that the specific exposures to tobacco and tobacco smoke constituent(s) or to combinations of those constituents that cause or contribute to tobacco-related chronic diseases are not known.[7] Implicit in the Guidance that a PMTA should include information on "... *whether such tobacco product presents less risk than other tobacco products...*" is the assumption that the relative risks to the smoker conveyed by any cigarette or another are knowable, quantifiable and comparable. The standards by which one cigarette may be scientifically concluded to present a similar, reduced or increased risk to the individual smoker relative to another cigarette have not been determined with certainty by any scientific or regulatory body. Although discussions of scientific standards for the comparisons of risks among tobacco products within a product category (e.g. among cigarettes) or between product categories (e.g. smokeless vs. cigarettes) are presently underway (http://iom.edu/Activities/PublicHealth/ModifiedRiskTobacco.aspx; http://lombardi.georgetown.edu/research/initiatives/tobacco/products.html), a consensus on the appropriate standards has not yet emerged and FDA has yet to provide its own views on those standards.

As discussed below, methods currently exist to compare chemical, biological and smoker exposure differences between cigarette products. Until scientific advances are made with respect to determining risks of smoking, FDA must rely on these currently existing methods for approval of PMTAs for new cigarette products.

The Guidance and the Act require that all available information on product design, composition, smoke yield (where applicable) and exposures resulting from the use of the new product be provided to FDA. The standard for approval of a new cigarette PMTA should be a demonstration that the new cigarette product is no more hazardous than cigarettes currently on the market based on appropriate product testing methods, as discussed below. Importantly, comparisons of individual and population risks for a new cigarette product must be developed from existing cigarette products, e.g. products of like design or smoke yield of tar and nicotine.

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[6] Recently, the National Academy of Sciences released its report to FDA regarding the Scientific Standards for Studies on Modified Risk Tobacco Products (available at www.nap.edu/catalog.php?record_id=13294. One commentator stated the following regarding the MRTP Standards: "Thus, it is virtually, if not literally impossible for any reduced risk product ever to be approved by the FDA under these scientific standards." Tobacco Analysis.blogspot.com 12/19/2011. Lorillard intends to provide comments to the recommended MRTP Standards at the appropriate time.

[7] Dorothy K. Hatsukami, Neal L. Benowitz, Stephen I. Rennard, Cheryl Oncken, Stephen S. Hecht. Biomarkers to assess the utility of potential reduced exposure tobacco products. Nicotine & Tobacco Research Volume 8, Number 4 (August 2006) 600–622.

Moreover, while allowing the introduction of new cigarette products which do not increase risk, FDA should actively encourage the introduction of new cigarette products which, even modestly, reduce smoker exposure and potential hazard, even if those products do not meet the higher standards of a MRTP. There has been a general downward trend in the sales-weighted average machine-measured tar yield of both established cigarette brands and newly introduced products over recent decades. The axiomatic principle of dose-response that serves as the foundation of modern pharmacology and toxicology suggests that encouragement of continuation of a downward trend in the yield of hazardous and potentially hazardous constituents is both consistent with, and necessary for, a reduction in the adverse public health impacts of cigarette smoking. FDA should follow the advice offered by the IOM in its 2001*Clearing the Smoke* report, *i.e.*, encourage and facilitate the introduction into the adult smoker marketplace products having a potential to reduce exposures and risks among users when accompanied by data that provides a reasonable assurance that the product's characteristics do not inadvertently elevate risks.[8]

A. Individual Exposure and Risk

The extensive knowledge in the areas of analytical chemistry, biomedical sciences and related disciplines as they relate to tobacco, cigarettes and cigarette smoke is documented in a vast literature of peer-reviewed, published work. For some decades now, a primary focus of much of the ongoing research conducted by cigarette manufacturers has been the adverse health effects related to smoking. This research has included improved methods to identify and quantify the tobacco and cigarette smoke constituents that are believed to be potential causes of the development of serious tobacco-related diseases.

In recent decades, cigarette manufacturers discovered the mechanism of the formation of tobacco-specific nitrosamines (TSNAs) during the flue-curing process that was formerly widely used in the United States. This discovery resulted in the adoption of a modified, indirect heating process that has substantially reduced the levels of TSNAs in contemporary U.S.-produced flue-cured tobaccos compared to those produced in earlier decades. The development and application of processes to expand the volume and filling value of cigarette tobaccos as a means to achieve lower masses of burned tobacco and concomitantly lowered yields of harmful or potentially harmful smoke constituents in consumer-acceptable cigarettes serves as another example of the immediate utility of new technologies to advance a potential incremental benefit to the public health. The question of whether such innovations may provide benefits that are sufficiently robust to qualify some cigarette products as MRTPs remains to be determined. Nevertheless, these examples suggest that incremental technological advances in the production of conventional new cigarette products have the potential to favorably impact the health of smokers by reducing some of the exposures to harmful and potentially harmful compounds in tobacco and cigarette smoke. The ability of tobacco manufacturers to quickly translate and apply such new scientific knowledge, discovery and innovation in the production of new cigarette products should not be constrained by an onerous, lengthy and impractically long pre-market qualification process that will serve to stifle, rather than foster such innovation.

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[8] Stratton, K., Shetty, P., Wallace, R., & Bondurant, S., (Eds.). (2001). Clearing the smoke: Assessing the science base for tobacco harm reduction. Institute of Medicine. Washington, DC: National Academies Press.

B. Population Exposure and Risk

The determinants of the health consequences associated with cigarette use are a product of genetics; environmental and lifestyle influences; cigarette design and composition; individual smoking intensity/topography, daily cigarette consumption, duration of lifetime cigarette use; and other societal and cultural influences. The regulation of cigarettes should be focused primarily on defined and measurable elements of the cigarette's design, composition and appearance.

An extensive history of hundreds of unsuccessful new cigarette product introductions by manufacturers speaks to the reality that these brands are often entirely unsuccessful in sustaining sales in the steadily-declining and intensely-competitive adult smoker marketplace. There is scant evidence that an excessively restrictive control of new cigarette product introductions will meaningfully reduce the population risks of smoking or provide benefits in terms of reduced tobacco initiation or increased cessation. The top 5 U.S. cigarette brand packings of U.S. cigarettes have been present in the marketplace for decades. The most recent new product introduction to have become established among the top 5 brands was Marlboro Gold (formerly Marlboro Lights) in 1980.[9]

II. Contents of a PMTA

The Guidance states:

> *Section 901(b)(1)(A) of the FD&C Act requires that a PMTA contain "full reports of all information, published or known to, or which should reasonably be known to the applicant, concerning investigations which have been made to show the health risks of such tobacco product and whether such tobacco product presents less risk than other tobacco products.*

and

> *For published studies concerning investigations which have been made to show the health risks of your tobacco product, you should provide a bibliography of the studies and an abstract for each study. You should also provide an explanation of the scope of the literature review you conducted to discover the relevant published studies, including how you identified, collect and reviewed the studies.*

As discussed above, the vast published studies on the health effects of cigarette smoking would make compliance with a literal reading of the Guidance unreasonably burdensome and practically impossible. FDA should clarify its interpretation of the Act to require the full reporting of all appropriate information with respect to the specific new cigarette product for

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[9] Manufacturer shipments to wholesalers data, provided to Lorillard as a subscriber, by Management Science Associates, Inc. (MSAI) of Pittsburgh Pennsylvania (YTD September 2011); The Maxwell Report Revised 1981 Year-End Sales Estimates For The Cigarette Industry (Lehman Brothers Kuhn Loeb Research), 2/1/82.

which the PMTA is submitted, rather than the submission of hundreds of thousands of pages of research on the health effects of cigarettes, generally.

The Guidance further states:

> *We request comment on what product chemistry, nonclinical, and adult human studies could be used to demonstrate that marketing of the product is appropriate for the protection of the public health. We also request comment on establishing a baseline for determining whether a new product affects the likelihood that tobacco users will quit or the likelihood that non-users will start using such products.*

The types and design of the studies necessary for approval of a PMTA must depend on the type of the new product. Chemistry, nonclinical and adult human smoker MLE (defined below) studies for a new cigarette product can demonstrate that the new product does not increase or reduces the exposure of smokers to cigarette smoke constituents of concern relative to existing products on the market.

A requirement for extensive human clinical biomarkers data for a new cigarette product that does not differ substantially from cigarettes legally marketed is unnecessary. The large smoker population sample sizes and extended time required to perform formal biomarkers analyses[10] render it impractical to perform full, formal assessments of exposure biomarkers on a pre-market basis. Data developed from human smokers requires recruitment of appropriate study populations that are representative of actual self-selected consumers of the product who are accustomed to it and who have chosen to use it in their normal manner. Previous forced brand switching studies have demonstrated study subjects substantively modify the manner and intensity of their smoking behaviors when switched to an unfamiliar new product.[11]

Recent progress toward validation of the emerging mouth-level exposure (MLE) methodology to estimate human smokers' exposures under real-world conditions of cigarette product usage may provide an effective and informative means for submitters and reviewers of PMTAs to provide information on smokers' exposures that will compliment data generated with machine smoking protocols.[12] The method has the potential to provide sufficient information on smokers' exposures from the use of a new conventional or near-conventional cigarette prototype to support FDA review of PMTAs in a reasonable time frame.

The Guidance also appears to contemplate the pre-market provision of information on a new product's performance in the marketplace as part of a PMTA. Specifically, information on a

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[10] Hans J. Roethig , Sagar Munjal , Shixia Feng , Qiwei Liang , Mohamadi Sarkar , Ruediger-A. Walk , & Paul E. Mendes. Population estimates for biomarkers of exposure to cigarette smoke in adult U.S. cigarette smokers. Nicotine & Tobacco Research, Volume 11, Number 10 (October 2009) 1216–1225.

[11] Mendes, P., Kapur, S., Wang, J., Feng, S., Roethig, H., A Randomized, Controlled Exposure Study in Adult Smokers of Full Flavor Marlboro Cigarettes Switching to Marlboro Lights or Marlboro Ultra Lights Cigarettes, Regulatory Toxicology and Pharmacology (2008), doi: 10.1016/j.yrtph.2008.04.014.

[12] Gregory M. Polzin , Weijia Wu , Xizheng Yan , Joan M. McCraw , Shadeed Abdul-Salaam , Ameer D. Tavakoli , Liqin Zhang , David L. Ashley , & Clifford H. Watson. Estimating smokers' mouth-level exposure to select mainstream smoke constituents from discarded cigarette filter butts. Nicotine & Tobacco Research Advance Access published June 18, 2009.

proposed new product's impact on initiation and cessation of tobacco use by non-users and users, respectively, could be required for FDA's approval of a PMTA. This illogical "Catch 22" requirement simply cannot be meaningfully measured and reported unless and until a product's performance in the free marketplace of adult smokers has been established in a nationally representative sample of smokers over several years. An extensive history of numerous examples of entirely unsuccessful market performance of new product introductions, that initially appeared likely to achieve market success in premarket evaluations, documents the relative imprecision and imperfect nature of available smoker preference evaluation tools that are available to the new product developer.

Furthermore, because new cigarette product introductions into a mature and declining market of competitive brand smokers are invariably accompanied by promotional activities intended to attract existing consumers of a competitor's brands to try the new product, the true market performance of a newly-introduced product simply cannot be meaningfully ascertained for some time (months to years) following its introduction. The potential appeal of a new cigarette product to existing non-users of tobacco, in particular, is simply indeterminable until those persons have made a decision to advance to regular cigarette use solely due to that particular new cigarette product. Pre-market focus groups may have some utility in projecting whether a new cigarette product would be anticipated to affect the rate of smoking initiation among non-smokers or to impair the rate of smoking cessation among smokers.

If sufficient flexibility in the required elements of a PMTA does not exist for approval of conventional new cigarette products, the market for cigarettes will be fixed and competition in this market will be constrained because no manufacturer will expend the resources necessary to bring a new cigarette product to market.

III. Suggested Clarifications

A. Clarification of use of GLPs

On page 13, the Guidance states:

> *Documentation of all actions taken to ensure the reliability of the study and the protection of human subjects – for example, documentation of study oversight by an Investigational Review Board (IRB) duly constituted and operating under 21 CFR Part 56, documentation of informed consent procedures such as appropriate procedures found in 21 CFR Part 50, and documentation of appropriate good laboratory practices such as those found in 21 CFR Part 58 (see additional details provided in section VII of this guidance);*

Good laboratory practices typically refer to the system of quality management of experimental (non-clinical) research studies. It is unclear whether FDA is recommending the use of GLPs in non-clinical studies of new tobacco products or whether the FDA intended to refer to the use of good clinical practices in the clinical studies of new tobacco products. FDA should revise the Guidance to clarify its intent with respect to this requirement.

B. Clarification of Timing

Page 8 of the Guidance, under "How Will We Review a PMTA?" states:

> *FDA will review your PMTA consistent with the requirements of section 910(c) of the FD&C Act. Under this section, FDA is required to review a PMTA "as promptly as possible, but in no event later than 180 days after the receipt of an application" (section 910(c)(1)(A)).*

Section 910(c)(1)(A) of the Act requires:

> *As promptly as possible, but in no event later than 180 days after the receipt of an application under subsection (b), the Secretary, after considering the report and recommendation submitted under subsection (b)(2), shall—*
>
> > *''(i) issue an order that the new product may be introduced or delivered for introduction into interstate commerce if the Secretary finds that none of the grounds specified in paragraph (2) of this subsection applies; or*
> >
> > *''(ii) issue an order that the new product may not be introduced or delivered for introduction into interstate commerce if the Secretary finds (and sets forth the basis for such finding as part of or accompanying such denial) that 1 or more grounds for denial specified in paragraph (2) of this subsection apply.*

The language in the Guidance could be read to mean that the FDA must begin review within 180 days of receipt of a PMTA, rather than the completion of FDA's review and issuance of an order no later than 180 days of receipt of the PMTA. FDA should revise the Guidance to remove this ambiguity.

C. Clarification of Referral to TPSAC

FDA should clarify that the 180-day period referred to in section 910(c)(1)(A) of the Act is not tolled by FDA's referral of a PMTA to TPSAC.

IV. Establishment of procedure to ensure opportunity for applicant interaction with FDA prior to PMTA submission

Although not required by the Act, Lorillard recommends that the FDA establish a procedure under which applicants who are considering submitting a PMTA are ensured an opportunity to meet with FDA on reasonably short notice and discuss the PMTA requirement for the particular new tobacco product prior to actual submission of the PMTA. The vast diversity of potential new tobacco products makes a "one size fits all" approach to PMTAs inappropriate. The competitive nature of the cigarette market also requires speed to market for any new cigarette product. The resources that would need to be devoted and the information that would need to be provided to demonstrate that a novel new tobacco product was "appropriate for the protection of

the public health" should differ dramatically from those needed to demonstrate that a new conventional cigarette product, employing no new technologies, should be approved by FDA for marketing. The Guidance provides no assistance in differentiating the requirements for very different new products. In the interest of employing both FDA's and the applicant's resources most efficiently and effectively, early discussions of the PMTA requirements are essential.

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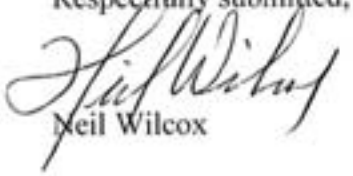
Lorillard appreciates the opportunity to submit these comments and looks forward to a continuing discussion with FDA regarding the PMTA process. Please do not hesitate to contact me if you would like to discuss any of Lorillard's comments.

Respectfully submitted,



Neil Wilcox