

October 11, 2011

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

Re: FDA-2011-N-0271 – Request for Comments on “Harmful and Potentially Harmful Constituents in Tobacco Products and Tobacco Smoke”

Introduction

Altria Client Services, on behalf of Philip Morris USA Inc. and U.S. Smokeless Tobacco Company¹; R.J. Reynolds Tobacco Company,² on behalf of itself, American Snuff Company LLC and Santa Fe Natural Tobacco Company, Inc.; and Lorillard Tobacco Company (collectively, the “Companies” or “We”) submit these comments to the Food and Drug Administration (“FDA” or “the Agency”) in response to the above captioned Notice requesting comments on “Harmful and Potentially Harmful Constituents in Tobacco Products and Tobacco Smoke.”³

Section 904(e) of the Federal Food, Drug, and Cosmetic Act, as amended by the Family Smoking Prevention and Tobacco Control Act (“Tobacco Control Act” or “the Act”),⁴ requires the FDA to establish, no later than April 2012, a list of all constituents identified by FDA as harmful or potentially harmful (“the HPHC list”) to health in each tobacco product, by brand and by quantity in each brand and subbrand. Implicit in 904(e) is a requirement for FDA to test and determine the quantity of each constituent on the HPHC list in each tobacco brand style currently sold in the United States because FDA has the initial obligation to list all HPHCs “by quantity in each brand and subbrand;” FDA cannot meet this obligation without testing and measuring. Thereafter, beginning in April 2013, manufacturers are required to test and report to FDA a list of constituents on the HPHC list in each of their respective tobacco products by brand and by quantity in each brand and subbrand.⁵

¹ Philip Morris USA (“PM USA”) and U.S. Smokeless Tobacco Company LLC (“USSTC”) are wholly owned subsidiaries of Altria Group, Inc. Altria Client Services (“ALCS”) is sending this letter on behalf of PM USA and USSTC. ALCS provides certain services, including regulatory affairs, to the Altria family of companies.

² R.J. Reynolds Tobacco Company (“RJRT”) bears primary responsibility for coordinating implementation of the Family Smoking Prevention and Tobacco Control Act for itself and Reynolds American Inc.’s other tobacco-manufacturing operating companies, namely American Snuff Company, LLC, and Santa Fe Natural Tobacco Company, Inc.

³ 76 Fed. Reg. 50,226-30 (August 12, 2011).

⁴ Family Smoking Prevention and Tobacco Control Act, Section 904(e), 21 U.S.C. §387d(e).

⁵ *Id.* at 904(a)(3), §387d(a)(3); The manufacturers' obligation to report HPHCs "by brand and quantity in each brand and subbrand" was delayed to April 2013 by operation of Sections 6(a) and (b) because that reporting is "contingent on" FDA's establishment of the HPHC list pursuant to Section 904(e). Had Congress not delayed the obligation, the manufacturers would be due to report in June 2012, an untenable proposition given the delay of FDA's establishment of the HPHC list until April 2012.

However, the regulations governing the “testing and reporting of . . . smoke constituents, by brand and subbrand that [FDA] determines should be tested to protect the public health”⁶ will not be promulgated under Section 915(a) until April 2013 -- the same date that manufacturers must begin reporting against the HPHC list. Thus, industry testing would have to occur long before FDA promulgates regulations that will presumably identify validated, standardized test methods and a focused list of HPHCs to be tested and reported. By April 2013, FDA is also required to publish the HPHC list “in a format that is understandable and not misleading to a lay person.”⁷

The order of this regulatory activity raises serious practical, scientific issues. It also exacerbates the companies’ shared concern about the need for accurate reporting of consistent, comparable data for regulatory purposes. Over time, the companies have gained substantial knowledge about the generation and interpretation of tobacco and smoke analytical data and believe this experience can help inform the Agency’s work in this area. In implementing Section 904(a) and (e), the companies urge the Agency to:

- 1) develop an initial list of constituents for testing and reporting purposes which represents the major classes of tobacco or smoke constituents;
- 2) lead a collaborative effort with industry, academic and testing laboratories to identify and develop validated and standardized testing methods for constituents included on the initial list; and
- 3) exercise its enforcement discretion to provide manufacturers with a minimum of one year after standardized methods are established to comply with Section 904(a)(3).

To assist the Agency in developing the initial HPHC list, the companies reference and incorporate their prior submissions and presentations relating to the development of the list.⁸ The companies also want to highlight three points made previously:

First, constituent lists developed to achieve a defined purpose can have some utility. The purpose of the list must be specific enough to enable scientifically-informed decision-making and should guide how FDA selects and quantifies various constituents. However, constituent lists will have limitations when applied beyond their defined purpose. For example, if the purpose of the list is to evaluate potential harm, then methods related to actual exposure in

⁶ Family Smoking Prevention and Tobacco Control Act, Section 915(b)(1), 21 U.S.C. §387o(b)(1).

⁷ *Id.* at 904(d)(1), §387d(d)(1).

⁸ Specifically, the companies incorporate herein Altria Client Service comments dated May 27, 2011, September 8, 2010, August 23, 2010 and an ALCS presentation by Dr. Jane Lewis during an open public hearing at the August 30, 2010 Tobacco Product Scientific Advisory Committee meeting; Lorillard comments dated August 30, 2010 and May 30, 2010; an industry presentation entitled “Preliminary Information Concerning the Establishment of a List of Harmful and Potentially Harmful Tobacco Product Constituents” delivered at the June 8-9, 2010 Tobacco Product Constituents Subcommittee meeting; and *Update (May/June 2011 Tobacco Regulation Issue): Establishing an FDA List of Harmful and Potentially Harmful Tobacco Product Constituents*, Ogden, M. at pages 10-15. (http://www.nxtbook.com/ygsreprints/FDLI/g19403fdli_nxtbook/#/12).

tobacco users and indirect exposure to non-tobacco users will provide more useful information than standardized machine methods. On the other hand, if the purpose of the list is to provide the public with a relative ranking of products, standardized machine methods will provide the most practical results. Defining the purpose is critical to developing a list that will be useful for regulatory purposes.

Second, certain of the companies urged the Agency to develop a definition of “harmful and potentially harmful constituents” that focused on those constituents that cause or have the potential to cause direct harm to the health of users and non-users of tobacco products. Instead, and contrary to Congressional intent, FDA indicated that its current thinking was to use a much broader definition that includes constituents that cause or have the “potential to cause indirect harm.” The Agency should amend its definition of “harmful and potentially harmful constituents” to align with Congressional intent and use that definition to develop the HPHC list.

Third, only properly validated and standardized measurement methodologies demonstrated to be fit-for-use and standardized across many laboratories can provide consistent and reliable information. A wealth of scientific literature shows that without validated and standardized methods, samples analyzed at multiple laboratories will vary even when using each individual laboratory’s validated methods (if they exist). This reality will make it difficult, if not impossible, to accurately make product comparisons, provide relevant consumer communications as contemplated by Section 904(d)(1), or make other regulatory decisions.

1. The Agency Should Develop an Initial HPHC List Which Represents the Major Classes of Tobacco or Smoke Constituents.

The companies urge the Agency to develop an initial HPHC list which represents the major classes of tobacco or smoke constituents. For example, when the World Health Organization (“WHO”) established its list of harmful constituents, it pared a potentially long list of smoke constituents to a shorter list it deemed useful for product monitoring. The resulting list represents the major classes of smoke constituents. The WHO list, or one developed with a similar logic, could serve as the Agency’s initial HPHC list for testing and reporting of cigarettes. Likewise, the same logic could be applied to smokeless tobacco constituents, with a list representing major classes of constituents such as tobacco-specific nitrosamines (“TSNAs”) and polycyclic aromatic hydrocarbons (“PAHs”).

Testing against an initial, more focused list of constituents within representative classes of HPHCs would be far more meaningful than attempting to test against the lengthy list proposed by the Agency. The proposed HPHC list includes many constituents that have been reported to be present in tobacco or tobacco smoke at exceedingly low levels near the limits of detection or quantification by current analytical chemistry methods. Additionally, many of the constituents included on the proposed HPHC list may be reasonably characterized as *de minimis* when their quantities and intrinsic toxicities are considered. The WHO included similar considerations when developing its list of priority toxicants.⁹ FDA can meet its statutory requirements and

⁹ See World Health Organization Technical Report 951: The Scientific Basis of Tobacco Product Regulation (2008).

objectives with a concise HPHC list of constituents that have been identified with confidence by multiple laboratories as being present in tobacco or tobacco smoke.

The proposed HPHC list far exceeds the breadth practical and appropriate for the FDA and manufacturers to measure and report harmful constituent levels in tobacco or smoke. The Agency bears the initial burden of testing and reporting against the HPHC list¹⁰ and then manufacturers must test and report thereafter. Both FDA and manufacturers will waste resources testing constituents for which there are not validated, standardized methods and scant evidence of either presence or biological relevance, at the levels present, in smoke or tobacco. The FDA should also keep in mind the limited number and capacity of manufacturer, commercial and government laboratories to perform extensive analyses that comply with contemporary data quality standards. All stakeholders, including both small and large manufacturers, will be affected by these capacity limitations. The available expertise will be far better utilized if the Agency focuses on an initial, more limited list of constituents for analysis.

2. FDA Should Lead a Collaborative Effort with Industry and Testing Laboratories to Identify or Develop Validated and Standardized Testing Methods.

FDA should lead a collaborative effort to identify or develop the methods to be used for testing and ensure that those methods are validated within laboratories and standardized across laboratories. Otherwise, testing will produce inconsistent and unreliable results.

FDA has recognized the importance of validating and standardizing methods in other contexts. For example, FDA's general draft guidance on analytical procedures and methods validation for drug substances and products clearly reflects the recognition of the importance and complexity of methods validation.¹¹ For purposes of an initial HPHC list, there are a number of ways to identify and establish validated, standardized methods. Existing organizations such as the American National Standards Institute (ANSI), the International Organization for Standardization (ISO), the U.S. Technical Advisory Group (U.S. TAG) to ISO, or the Cooperation Centre for Scientific Research Relative to Tobacco (CORESTA) could help facilitate this effort with FDA playing a lead role. The FDA Modernization Act of 1997 authorizes FDA to participate in such activities and the Agency's leadership in this effort will be critical. Any of these approaches would provide a transparent, scientifically grounded process. Ideally, the methods developed in this process would be adopted as approved regulatory methods, thus providing clarity and efficiencies for the FDA, manufacturers and laboratories.

The application of validated, standardized methods is critical to make a useful comparison of constituent yields from different tobacco products over time in different laboratories. Existing standardized analytical methods for constituents on the proposed HPHC list are currently insufficient to provide reliable data. Even within a laboratory where validated methods exist, considerable methodological variability occurs. As relates to cigarettes, there are three primary reasons that analytical measurements of smoke constituents differ within and across labs: 1) low

¹⁰ See §904(e) ("Not later than [April 1, 2012], the Secretary shall establish, and periodically revise as appropriate, a list of harmful and potential harmful constituents, including smoke constituents, to health in each tobacco product by brand and by quantity in each brand and subbrand.").

¹¹ <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM122858.pdf>.

levels of constituents present in smoke; 2) sample variability; and 3) method variability. The companies provide specific examples of this variability in Attachment A. A collaborative effort between FDA, manufacturers and laboratories will be essential to understanding method variability and establishing standardized methodologies.

While standardizing the analytical methods, the smoking machine regimens used to generate and measure HPHCs must be defined. The TPSAC recommended testing using two smoking regimes – ISO and Canadian Intense. It is not clear from the Notice for Comment if FDA is proposing to accept this recommendation. Nevertheless, if TPSAC based its recommendation on an assumption that more data from two different methods is superior in some way to a single, well-established protocol, that assumption is not correct. For example, the analytical results measured using the Canadian Intense regimen may not be useful or informative in making comparisons between cigarettes of varying design and composition.¹² Analysts may have a difficult time making such comparisons due to the simultaneous imposition of differences in puff frequency and volume, combined with the partial or complete elimination of the filter ventilation/dilution element of a given cigarette design.¹³ Additionally, analytical methods using the Canadian Intense regimen have not been standardized.¹⁴ For initial product reporting and comparison purposes, the FDA can and should meet its existing statutory obligations by requiring testing and reporting based on the ISO smoking regime alone. Any HPHC list developed for other purposes would require an evaluation of which smoking machine method or methods would be best suited to the purpose of the list.

3. The Agency Should Exercise its Enforcement Discretion to Provide Manufacturers with a Minimum of One Year After Standardized Methods are Established to Comply with Section 904(a)(3).

Manufacturers must comply with Section 904(a)(3) beginning April 2013, the same date FDA will promulgate regulations governing the “testing and reporting of . . . smoke constituents, by brand and subbrand that [FDA] determines should be tested to protect the public health.”¹⁵ As noted above, these regulations will presumably identify validated, standardized test methods and identify a focused list of HPHCs that must be tested and reported. Requiring testing and

¹² See Roemer E., and Carchman R.A. (2011). Limitations of cigarette machine smoking regimens. *Toxicology Letters* 203(1):20-27.

¹³ *Id.*

¹⁴ Analytical methodologies must be validated within labs and standardized across labs to ensure key analytical parameters such as trapping efficiencies with impingers are characterized. While methods exist under the ISO smoking regimen to determine several constituents, these methods have not been standardized under the Canadian Intense smoking regimen. Differences between types of smoking machines will also need to be characterized using the Canadian Intense smoking regimen. Validated, standardized methods for identification and quantification of HPHC are also impacted by the smoking regimen selected for analysis. In April, 2011 a CORESTA subgroup, the CORESTA Special Analytes Task Force (SATF), discussed establishing CORESTA Recommended Methods (CRM) for volatiles, carbonyls and PAHs under Health Canada smoking conditions. Participating laboratories were asked to provide information on any modifications necessary to ensure trapping efficiencies were reliable under intense smoking conditions. Additionally, laboratories have been asked to provide data on intense smoking conditions for several reference cigarettes for comparison. As a preliminary study, data collection will not begin until 2012.

¹⁵ Family Smoking Prevention and Tobacco Control Act, Section 915(b)(1), 21 U.S.C. §387o(b)(1).

reporting before these regulations are in place is illogical and, if required, likely to produce data that will be confusing and not useful for product comparisons or other regulatory purposes. Therefore, the companies urge the Agency to publish its intent to exercise enforcement discretion to provide manufacturers with a minimum of one year after validated, standardized methods are established to comply with Section 904(a)(3).

Conclusion

We appreciate the opportunity to submit these comments and urge the Agency to incorporate them as it develops the HPHC list. We look forward to further opportunities to work with FDA on this important issue.

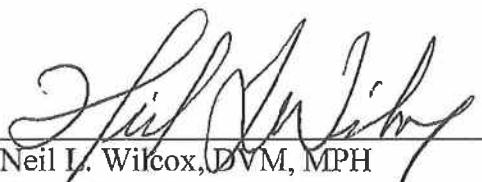
Sincerely,



James E. Dillard, III
Senior Vice President, Regulatory Affairs
Altria Client Services



Michael W. Ogden, Ph.D.
Senior Director, Regulatory Oversight
R.J. Reynolds Tobacco Co.



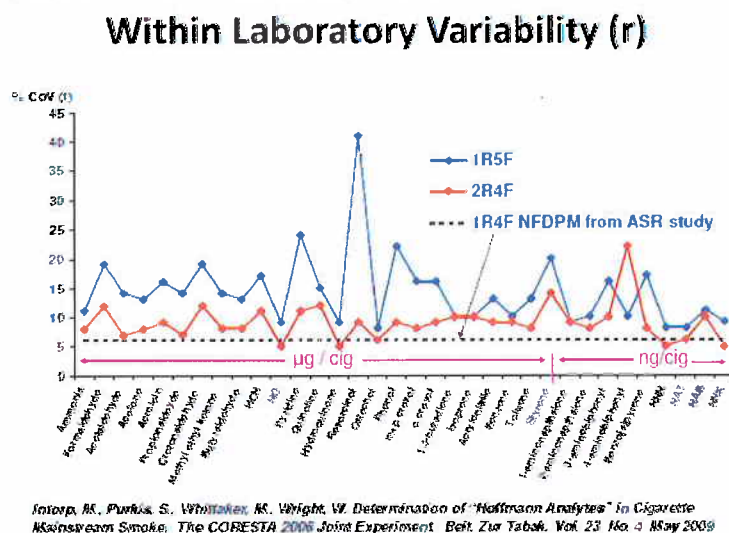
Neil L. Wilcox, DVM, MPH
Senior Vice President and Chief Compliance Officer
Lorillard Tobacco Company

ATTACHMENT A

Within laboratory variability (r) and between laboratory variability (R) are limits which are characterized using specifically designed studies as part of the standardization process. The within laboratory variability (r) and between laboratory variability (R) limits specify the maximum difference between results which can be reasonably attributed to the method variability. The (r) and (R) variability limits, therefore, may be used to understand whether observed differences in analytical results generated in multiple, or single, laboratories are in fact due to differences in the sample or a result of within or between laboratory variability. In the absence of defined within and between laboratory variability limits, data generated at multiple laboratories, and in some cases at single laboratories, can be indistinguishable and therefore potentially meaningless.

In 2009, Intorp *et al.* reported on joint experiments conducted in 19 laboratories for a CORESTA study to determine variability in the determination of certain Hoffmann List analytes under ISO smoking conditions.¹⁶ Each laboratory analyzed the 2R4F and 1R5F reference cigarettes using its own in-house methodology for each Hoffmann analyte. Figure 1, below, shows the within laboratory variability (r) for 34 mainstream smoke constituents for the 1R5F, an approximately 2 mg/cigarette ISO “tar” reference cigarette, (blue) and the 2R4F, an approximately 9 mg/cigarette ISO “tar” reference cigarette, (red) reference cigarettes. For the 2R4F, the within laboratory variability at one point in time ranged between 5 and 20% with most analytes being between 5 and 10%. For the 1R5F, the within laboratory variation increased for most analytes with the (r) ranging from approximately 7% for TSNAs to about 20% for several volatile compounds.

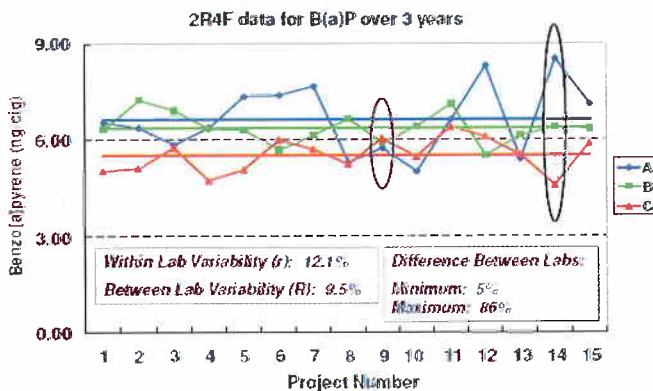
Figure 1, Within Laboratory Variability (r)



¹⁶ See Intorp, M., Purkis, S.W., Whittaker, M.W., Wright, W., (2009). Determination of “Hoffmann analytes” in mainstream cigarette smoke. *Beiträge zur Tabakforschung International* 23(4), 161-202.

Figure 3, Between Laboratory Variability Over Time (BaP)

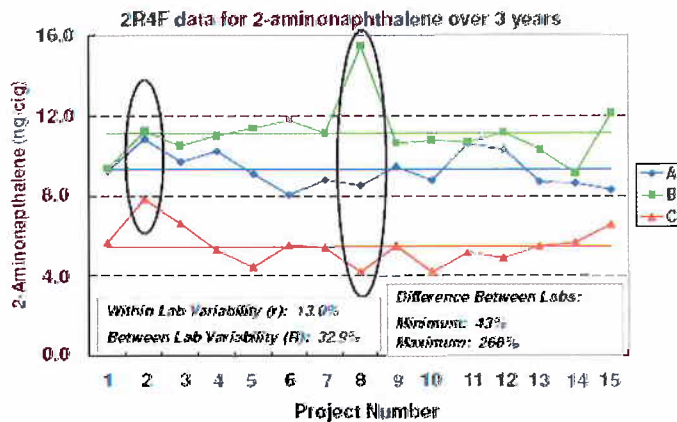
Between Lab Variability Over Time



Hyodo, T., Inoue, O., Katagiri, H., Niikita, A., Fujiwara, M.: Long-term Interlaboratory Comparisons of Selected Smoke Analytes in 2R4F Mainstream Smoke, 2006 CORESTA Congress, Japan Tobacco Inc.

Figure 4, Between Laboratory Variability Over Time (2-aminonaphthalene)

Between Lab Variability Over Time



Hyodo, T., Inoue, O., Katagiri, H., Niikita, A., Fujiwara, M.: Long-term Interlaboratory Comparisons of Selected Smoke Analytes in 2R4F Mainstream Smoke, 2006 CORESTA Congress, Japan Tobacco Inc.

Figure 3, above, indicates that data generated over time using a standardized method for B(a)P in any single laboratory would be similar to data generated across multiple laboratories (i.e., R is close to r). Thus, when comparing data between laboratories using standardized methods one could make reasonable conclusions regarding observed sample differences and method variability. However, as illustrated in Figure 4, the use of the non-standardized method for 2-aminonaphthalene increased the between laboratory variability (i.e., R is not close to r). In this case, one could not reasonably differentiate sample difference and method variability.