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June 1, 2012

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

Re: Docket No. FDA-2012-D-0049 – Comments on Draft Guidance Entitled "Reporting Harmful and Potentially Harmful Constituents in Tobacco Products and Tobacco Smoke Under the Federal Food, Drug, and Cosmetic Act"

Altria Client Services Inc. ("ALCS"), on behalf of Philip Morris USA Inc. ("PM USA") and U.S. Smokeless Tobacco Company LLC ("USSTC"),[1] submits these comments regarding the Food and Drug Administration's ("FDA" or "the Agency") above-captioned draft guidance document ("Draft Guidance").

Section 904(e) of the Federal Food, Drug, and Cosmetic Act, as amended by the Family Smoking Prevention and Tobacco Control Act ("FSPTCA" or "the Act"),[2] requires FDA to establish, no later than April 2012, a list of all constituents identified by FDA as harmful or potentially harmful ("the HPHC list") in tobacco products and tobacco smoke. On March 30, 2012, FDA established its HPHC list, which consists of 93 constituents.[3] FDA also issued Draft Guidance related to testing and reporting against the HPHC list.

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[1] PM USA and USSTC are wholly-owned subsidiaries of Altria Group, Inc. ("Altria"). ALCS provides certain services, including regulatory affairs, to the Altria family of companies. "We" and "our" are used throughout to refer to PM USA and USSTC.

[2] FSPTCA, Section 904(e), 21 U.S.C. §387d(e).

[3] As relates to the establishment of the HPHC list, we specifically reference and incorporate our prior submissions and presentations, including joint comments submitted by ALCS, R.J. Reynolds Tobacco Company and Lorillard Tobacco Company dated October 11, 2011; ALCS comments dated May 27, 2011, September 8, 2010, and August 23, 2010; an ALCS presentation by Dr. Jane Lewis (ALCS Senior Vice President, Tobacco Regulatory and Health Sciences) during an open public hearing at the August 30, 2010 Tobacco Product Scientific Advisory Committee meeting; and 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.

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We are encouraged that the Draft Guidance recognizes the importance of using well established and widely available testing methods in establishing an abbreviated HPHC list of 20 constituents for initial testing and reporting purposes. The abbreviated HPHC list appropriately represents several different chemical classes of HPHC found in tobacco and smoke.

The development of validated and standardized methods for any constituent testing, however, remains a critical need. Without validated and standardized methods, constituent testing and reporting will necessarily be of limited utility because the data will be inconsistent and unreliable for product comparisons or other decision making. For cigarette smoke testing under the ISO smoking conditions, only 14 of the 18 constituents on the abbreviated HPHC list have standardized test methods developed through a Voluntary Consensus Standards process. There are no standardized methods for the Canadian Intense smoking condition. For tobacco (both smokeless and tobacco used in cigarettes[4]), it is only three out of nine. Unfortunately, needed standardized methods cannot be developed prior to the September 2012 reporting deadline.

Moving forward, one of the Agency's first priorities should be to lead a collaborative effort to develop Voluntary Consensus Standards for testing HPHC for which there are no standardized methods. Section 915 of the Act requires FDA to promulgate, no later than April 2013, regulations governing the "testing and reporting of . . . smoke constituents, by brand and subbrand that [FDA] determines should be tested to protect the public health."[5] We urge FDA to address the issue of method standardization in any regulations the Agency promulgates under Section 915.

The Draft Guidance also correctly recognizes the relatively short time that manufacturers have to test and report in order to comply with the September 22, 2012 deadline,[6] even with an abbreviated HPHC list. The Draft Guidance, however, provides no indication of the timing, scope or frequency of any future testing. As FDA considers future testing, it is important for the Agency to take into account the extensive time, planning and resources needed for manufacturers to comply.

Our comments to the Draft Guidance address the following topics:

I. FDA Should Lead a Collaborative Effort to Develop Voluntary Consensus Standards;
II. Tobacco Reference Products Should Be Used for Analytical Testing;
III. Testing Three Replicates is Sufficient to Produce Meaningful Data;
IV. FDA Needs to Establish Method Validation Guidelines;
V. Testing of Roll-Your-Own Tobacco Products Should Include Analysis of Smoke; and
VI. FDA Should Enhance the Functionality of the e-Submitter Tool and the Reporting Template

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[4] This includes filler used in manufacturing cigarettes, roll-your-own tobacco and cigarette tobacco.
[5] FSPTCA, Section 915(a) and (b)(1), 21 U.S.C., §387o(a) and (b)(1).
[6] The September 22, 2012 deadline is more reasonable than a June 22, 2012 deadline. We reiterate, nevertheless, that 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) of the Act because that reporting is "contingent on" FDA's establishment of the HPHC list pursuant to Section 904(e).

I. FDA Should Lead a Collaborative Effort to Develop Voluntary Consensus Standards

FDA should lead a collaborative effort to identify and develop Voluntary Consensus Standards for constituents testing and ensure that these testing methods are validated within laboratories and standardized across laboratories. Ideally, FDA would have initiated this effort prior to requiring any HPHC testing. While method standardization cannot be achieved for all 20 constituents prior to the 2012 reporting deadlines, it should be a priority before FDA requires additional constituents testing. FDA should interpret the 2012 results with caution given issues with the lack of method standardization. As noted above, we urge FDA to recognize the importance of method standardization in any regulations it promulgates under Section 915 and to keep in mind that the ISO and Canadian Intense smoking methods are different and need to be validated and standardized as such.

FDA, manufacturers, and testing laboratories have a mutual interest in ensuring that analytical testing data are reproducible and comparable across laboratories (i.e., data of known quality). Otherwise, testing will produce inconsistent and unreliable results for product comparison or other decision making. Existing organizations such as the American National Standards Institute ("ANSI"), the International Organization for Standardization ("ISO"), the U.S. Technical Advisory Group to ISO/Technical Committee 126 ("U.S. TAG") or the Cooperation Centre for Scientific Research Relative to Tobacco ("CORESTA") could help facilitate this effort. The FDA Modernization Act of 1997 authorizes FDA to participate in such activities and the Agency's leadership in this effort will be critical.

FDA collaboration with any of these standards organizations would provide for 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 contract laboratories. 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.[7] The application of validated, standardized methods is critical to make a useful comparison of constituent yields from tobacco products over time and/or in different laboratories.

II. Tobacco Reference Products Should Be Used for Analytical Testing

The Draft Guidance does not address the use of tobacco reference products in this initial round of HPHC testing. Given the rapidly approaching September 2012 reporting deadline and on-going testing by manufacturers, it is unlikely that FDA can fully address this issue in the Final Guidance. We raise the issue now to urge FDA to consider the role of tobacco reference products in future HPHC testing.

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[7] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM122858.pdf

Laboratories should use existing tobacco reference products as part of any analytical testing program because such products can be used to compare analytical results from different laboratories at a single point in time as well as across laboratories over time. Cigarette and smokeless tobacco reference products – consistent in content and construction – have been widely used by manufacturers and private and government laboratories over an extended period of time for monitoring analytical testing performance. The ability to accurately compare HPHC data generated by multiple laboratories for multiple companies' products (by brand and subbrand) during a single reporting cycle – and to monitor products over time – requires reliable reference data that tobacco reference products can provide.

The Kentucky Reference Cigarette ("KRC") is sponsored and maintained by the University of Kentucky's ("UK") Tobacco and Health Research Institute. First introduced in the late 1960's beginning with the 1R1, an unfiltered cigarette, KRCs have evolved over time to reflect cigarette products in the marketplace in terms of smoke yield, construction and tobacco blend. Currently available 3R4F and 1R5F cigarettes are filtered 10 mg and 2 mg tar cigarettes, respectively (as measured by the ISO smoking protocol).

The North Carolina State University Tobacco Analytical Services Laboratory ("TASL") is the central repository for a series of Smokeless Tobacco Reference Products ("STRP") and CORESTA[8] Reference Products ("CRP"). STRPs, first manufactured in 1986, are similar to current CRPs (with the exception of the newly introduced snus CRP).

Given extensive laboratory experience using these existing tobacco reference products, we urge FDA to require the use of 3R4F and 1R5F and CRPs for constituents testing for cigarettes and smokeless tobacco products, respectively. Testing laboratories should test the appropriate reference products for the required FDA HPHC list and report those results along with the HPHC data from commercial products using validated analytical methods. Doing so will help FDA determine whether the analytical laboratories engaged in HPHC testing are producing comparable results.

As users exhaust existing supplies of tobacco reference products, a manufacturer will have to produce new reference tobacco products. Since tobacco chemistry varies with tobacco type, these new tobacco reference products, like existing tobacco reference products, should contain the major types of tobacco used in U.S. commercial products (e.g., bright, burley and oriental). Such products should be suitable for use as part of HPHC testing. To ensure high quality, a reputable manufacturer should make the tobacco reference materials.

Neither manufacturers nor standards organizations have certified most existing tobacco reference products; therefore, we urge FDA to establish a certification process for such products as manufacturers produce new tobacco reference products. Certified reference products will allow testing laboratories to verify the performance of their analytical procedures – a critical component for FDA to obtain representative and comparable data about the commercial products sold on the

[8] Cooperation Centre for Scientific Research Relative to Tobacco.

U.S. market. *ISO Guide 35: Reference Materials – General and Statistical Principles for Certification* provides useful guidance that FDA should consider.

Certification of each reference product production lot will provide a means of maintaining the historical comparability of HPHC data. Certified reference products would also facilitate the establishment of validated HPHC analytical methods in laboratories and in conducting performance evaluations of laboratories. FDA could work with existing U.S. based organizations such as the U.S. TAG, contract laboratories, academic groups, American Society for Testing and Materials ("ASTM"), National Institute of Standards and Technology ("NIST") and tobacco product manufacturers to design, produce, certify and distribute tobacco reference products that could support HPHC testing requirements.

III. Testing Three Replicates is Sufficient to Produce Meaningful Data

Testing three replicates is generally sufficient for most tobacco and smoke constituents. Additional replicates are typically not worthwhile because they produce little improvement in the quality of the data. FDA should, therefore, recommend in its Final Guidance that manufacturers test three replicates for each constituent instead of the seven (or 20 for nicotine and carbon monoxide) in the Draft Guidance.

Laboratory analytical testing very often demonstrates greater variability over longer periods of time.[9] A nested variance component model can be used to approximate over time variance. This model, which reflects a common statistical approach, incorporates both short-term and long-term variance components σ_{ST}^2 and σ_{LT}^2, respectively. Using the mean value of the (n) replicates, the associated standard deviation is calculated using the following equation:[10]

$$\sigma_{TR} = \sqrt{\sigma_{LT}^2 + \frac{\sigma_{ST}^2}{n}} \qquad (1)$$

The over time variability of laboratory test results supports the following two conclusions:

- For most constituents, it is adequate to perform three replicates. Additional replicates only reduce the short-term component in the standard deviation and, therefore, have a limited effect on the overall uncertainty of the associated test result. The larger the ratio becomes between the long-term and short-term variance components, the less the improvement additional replicates provide in reducing the overall variability. Table 1 demonstrates the minimal difference between test results comparing three or seven replicates.

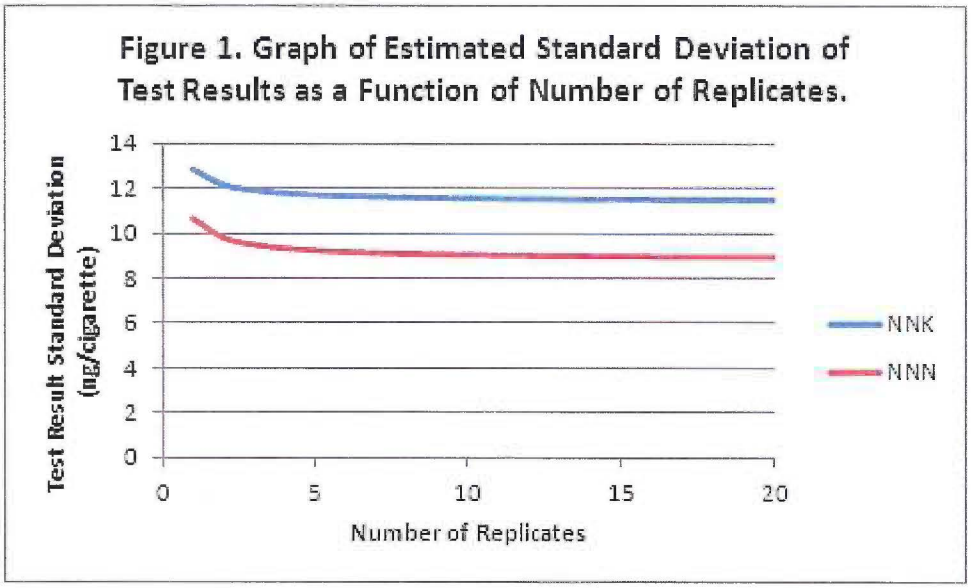
[9] Morton MJ and Laffoon SW, 2008. Cigarette smoke chemistry market maps under Massachusetts Department of Public Health smoking conditions. Regulatory Toxicology & Pharmacology. 51:1–30. See Appendix B in particular.
[10] We estimated those terms using a nested analysis of variance model from historical 2R4F analytical data for the constituents in Table 1.

- Table 1 shows that if the uncertainty in the test result is estimated from the standard deviation of the sample replicates, only the short-term uncertainty is captured. In order to capture the overall uncertainty, the estimated standard deviation should incorporate an estimate of long-term method variation. This can be achieved by using long-term historical data from the test laboratory or from inter-laboratory studies.

Table 1.

Analyte	σ_{LT}^2	σ_{ST}^2	σ_{TR} 3 reps	σ_{TR} 7 reps	Within Sample Std Err 3 reps	Within Sample Std Err 7 reps
1,3-Butadiene (ug/cig)	38.2	6.13	6.34	6.25	1.43	0.94
Acetaldehyde (ug/cig)	1217	2631	45.8	39.9	29.6	19.4
Acrolein (ug/cig)	16.8	25.4	5.03	4.52	2.91	1.90
Acrylonitrile (ug/cig)	0.620	0.235	0.84	0.81	0.28	0.18
Benzene (ug/cig)	12.0	6.1	3.75	3.59	1.43	0.93
Benzo(a)pyrene (ng/cig)	0.401	0.122	0.66	0.65	0.20	0.13
Carbon Monoxide (mg/cig)	0.178	0.245	0.51	0.46	0.29	0.19
Crotonaldehyde (ug/cig)	6.06	3.22	2.67	2.55	1.04	0.68
Formaldehyde (ug/cig)	8.86	6.45	3.32	3.13	1.47	0.96
Isoprene (ug/cig)	889	444	32.2	30.9	12.2	8.0
Nicotine (mg/cig)	0.00060	0.00099	0.031	0.027	0.018	0.012
NNK (ng/cig)	130.0	35.0	11.9	11.6	3.42	2.24
NNN (ng/cig)	78.1	35.4	9.48	9.12	3.43	2.25
Tar (mg/cig)	0.158	0.191	0.47	0.43	0.25	0.17
Toluene (ug/cig)	40.3	20.9	6.88	6.58	2.64	1.73
σ_{LT}^2 and σ_{ST}^2 are estimated from historical data. σ_{TR} estimated from equation (1).						

As an example, Figure 1 below illustrates the relationship between the number of replicates and the standard deviation of the associated test result for NNK and NNN.



Based on the analysis above, FDA's Final Guidance should recommend that manufacturers test three replicates for each constituent instead of the seven (or 20 for nicotine and carbon monoxide) in the Draft Guidance as the least burdensome approach.

IV. FDA Needs to Establish Method Validation Guidelines

FDA needs to establish method validation guidelines to ensure that laboratories use validated and standardized methods to test for HPHC. The scope and content of those guidelines should explicitly define stakeholders, method type (e.g., qualitative, semi-quantitative, quantitative), validation parameters required, acceptance criteria for each validation parameter and the testing necessary to satisfy the validation parameter.

V. Testing of Roll-Your-Own Tobacco Should Include Analysis of Smoke

The Draft Guidance requires testing of roll-your-own ("RYO") tobacco and filler, not smoke from the made cigarette.[11] To mitigate consumer confusion, FDA should state in its Final Guidance

[11] *See, e.g.*, Draft Guidance at 4-5. Retailers engaged in RYO operations are cigarette manufacturers subject to FDA's jurisdiction; *see also* ALCS letter dated February 13, 2012 to Ele Ibarra-Pratt, RN, MPH, Office of Compliance and Enforcement with the Center for Tobacco Products re: roll-your-own machines at retail.

that RYO or any loose tobacco used to make cigarettes is subject to the same requirements as other cigarettes, including testing smoke.[12]

VI. FDA Should Enhance the Functionality of the eSubmitter Tool and the Reporting Templates

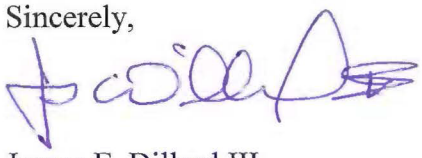
The Draft Guidance recommends that manufacturers use the eSubmitter tool to submit HPHC reports.[13] FDA has also posted templates to report HPHC data.[14] We urge the Agency to configure the eSubmitter tool and reporting templates so manufacturers can report constituent levels that are below the detection limit of the method (BDL) or where the constituent testing results may be at the lower limit of quantitation (LLOQ) of the method. Specifically, we recommend eSubmitter either allow character values, such as "BDL" or "LLOQ," or the adoption of a numeric code such as "0" or "-1" to indicate non-quantitative data.

FDA's Final Guidance should include instructions for reporting these types of analytical results well in advance of the September 2012 deadline so that manufacturers have adequate time to prepare and file their HPHC reports.

Conclusion

We appreciate the opportunity to submit these comments and urge the Agency to incorporate them in its Final Guidance.

Sincerely,



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[12] ISO has established methods to test tobacco and smoke in RYO: ISO 15592-1:2001 - "Fine-cut tobacco and smoking articles made from it -- Methods of sampling, conditioning and analysis -- Part 1: Sampling;" ISO 15592-2:2001 - " Fine-cut tobacco and smoking articles made from it -- Methods of sampling, conditioning and analysis -- Part 2: Atmosphere for conditioning and testing;" ISO 15592-3:2008 - "Fine-cut tobacco and smoking articles made from it -- Methods of sampling, conditioning and analysis -- Part 3: Determination of total particulate matter of smoking articles using a routine analytical smoking machine, preparation for the determination of water and nicotine, and calculation of nicotine-free dry particulate matter"

[13] Draft Guidance at 9-10.

[14] http://www.regulations.gov/#!documentDetail;D=FDA-2012-D-0049-0003.