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Acceptable Analytical Methods for Assessing the Quantity of Each Constituent

Comments presented at the Tobacco Product Constituents Subcommittee of the Tobacco Products Scientific Advisory Committee
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RE: **Acceptable analytical methods for assessing the quantity of each constituent**

Arista Laboratories, Inc. is an independent and ISO 17025:2005 accredited (A2LA) laboratory specializing in the analysis of tobacco, tobacco products and smoke constituents. Arista's independent nature means that we accept contracts from all parties including tobacco manufacturers, regulators, academics and others with an interest in high quality analytical results.

We are a member of CORESTA, NCI's Tobacco Products Assessment Consortium (TobPRAC), ASTM and the US Technical Advisory Group to ISO Technical Committee 126.

My comments today are made in my capacity as President of Arista Laboratories, Inc.

I have four key points that I would like to make today that are:

1. Analytical methods should not be prescribed by law.
2. A defined quality system is necessary
3. Machine smoking conditions must be clearly defined
4. Replicate requirements need to be explicitly stated

- **Analytical methods should not be prescribed by law.**

  Methods validated through the process of collaborative study procedures (AOAC International, 2002) are valuable reference documents to analytical laboratories and form in many cases the basis of accreditation for the analysis of specific compounds. Collaborative studies are conducted through a process requiring cooperation and support from a minimum of ten laboratories, conducted at great expense and over a long period of time. Results from collaborative studies are published and made generally available by standards organizations. Relevant methods for tobacco and smoke constituents can be found from the International Organization for Standardization (ISO) but only six methods are published for the analysis of constituents in mainstream cigarette smoke covering a narrow range of analytes (tar, nicotine, carbon monoxide, water, alkaloids, benzo[a]pyrene).

  The continued development of ISO methodology relevant to cigarette products is in the interest of groups such as the Cooperation Centre for Scientific Research Relative to Tobacco (www.coresta.org) and WHO's Tobacco Laboratory Network (TobLabNet). Both groups are active in promoting methodology to ISO but are of limited productivity given the lengthy collaborative process. Establishment of methods suitable to address all of the constituents of likely interest to the FDA will require many more years, if not decades, to complete.

  Other method sources from various publications such as the Health Canada Tobacco Reporting Regulations, the Centers for Disease Control, ASTM International or WHO's TobReg do not necessarily utilize the collaborative study approach to verify methodology. This presents

methods from a single perspective without the benefit of peer review. It is not unusual for published methods to contain conflicting detail, insufficient descriptions or fully erroneous information that prevents the verbatim execution of the method. Codifying such methods, as in the case of Health Canada's TRR, presents a situation whereby the laboratory may be technically forced to violate the law in order to complete the analysis. Absent the type of data completed in a collaborative study, that is, the statistics suitable to evaluate improvements in specificity, accuracy, precision and other metrics vital to interpreting results, data collection becomes data collection for its own sake and does not provide a framework by which product standards can be developed when they are not. We do not favor prescriptive and codified methods that inhibit the development of new technology.

Laboratories should have the freedom to improve methodology, utilize state-of-art technology and improve operational costs as available. Accordingly, Arista Laboratories favors an approach to analytical methodology that relies upon sound principles of validation such as those found in the International Committee on Harmonization (ICH Harmonised Tripartite Guideline, 2005) or the FDAs Guidance for Industry Bioanalytical Method Validation (HHS, Food and Drug Administration, May 2001) and open to inspection by a third party authority.

- **A defined quality system is necessary**

Independent third party accreditation to an internationally accepted standard such as ISO 17025:2005 supports a level of competency across the range of analytical methods for the testing of tobacco products. Scheduled and periodic review of a laboratory's quality system through the accreditation process encourages an environment of continuous improvement in systems and management.

Commercial and industry laboratories presently exist that are accredited to perform the analysis of tobacco products, including smoke constituents, in conformance with the ISO 17025:2005 laboratory standard. In many cases, the methods listed on the respective scopes of accreditation have been the subject of industry collaborative studies, reflect years of analytical expertise in the field of tobacco analysis and are optimized, rugged and free of interferences – requirements of an optimized method.

An alternative to accreditation is conformance to *current* Good Laboratory Practices (cGLP) consistent with the regulation of pharmaceuticals, food and pesticides. Laboratories that have the competency to perform the analysis of tobacco products, including smoke constituents have not undertaken the burden of cGLP because of the advent of ISO 17025 as a superior quality management practice fit for the purpose of tobacco products analysis. Furthermore, the industry-unique equipment used for the machine smoking of tobacco products does not conform to cGLP principles and will take time to establish. FDA must understand that the demand for such equipment is very much smaller than in other industries such as food, the environment and pharma, and the market demand for such equipment is declining with the consolidation of the industry and the rationalization of products. Inspiring instrument

manufacturers to re-work their equipment to a cGLP standard will come at significant expense to a few laboratories such as Arista and will delay the ability to comply with the Act.

We fully support a quality standard such as ISO 17025:2005 and accreditation through third party, independent, organizations. We do not support a cGLP requirement.

- **Machine smoking conditions must be clearly defined**

  It is understood that machine smoking methods are not representative of human smoking behavior. However, cigarette smoking conditions must be uniform across laboratories for results to be comparable over time and useful in establishing a product standard and interpreting product trends. Such conditions should include parameters such as those found in the ISO standards or as published in the Health Canada TRR with reference to the ISO standards.

- **Replicate requirements need to be explicitly stated**

  Natural products are inherently variable despite mass production under seemingly uniform conditions. The variability arising from the products, combined with variability in machine smoking prior to analysis, makes it imperative that a sufficient number of replicate analyses are conducted to give statistical significance to the final data. The number of replicates should be clearly stated in the testing requirements and relate to the form of the product under consideration. That is, tobacco constituents may have a different number of replicates than smoke constituents. For example, it should be noted that the Health Canada TRR prescribes 7 replicates for smoke analysis and 3 replicates for tobacco. We agree with this approach.

  We encourage FDA to consider setting replicates required for all smoke constituents at the same number to facilitate laboratory optimization and allow correlation between constituents as products evolve. This has not always been the case for the Health Canada TRR, the Massachusetts Department of Health or the Federal Trade Commission reporting where the number of replicates for tar, nicotine and carbon monoxide are set at 20 replicates while other analytes are at a lesser number (e.g. 7 replicates).

Conclusion

The time table for reporting as defined in the Act is a short 12 months after the publication of the list of harmful and potentially harmful constituents. Establishing laboratory capacity for completing this work at any level is a challenge and I would encourage this committee and the FDA to work toward the early establishment of the list of constituents and the testing requirements.

Thank you for the opportunity to speak today.