Recent Advances In Tobacco Science

Volume 44

Building Science and Evidence in the Regulated Tobacco Landscape

Symposium Proceedings
72nd Meeting
TOBACCO SCIENCE RESEARCH CONFERENCE

September 16-19, 2018
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Symposium of the 72nd Tobacco Science Research Conference

Building Science and Evidence in the Regulated Tobacco Landscape

– Symposium Chair –
Kathy Humphries

– Editors –
Jason Flora
Summer Hanna
Kathy Humphries

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72nd Tobacco Science Research Conference

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PREFACE

The Program Editorial Committee of the 72nd Tobacco Science Research Conference is pleased to present the 44th volume of the Recent Advances in Tobacco Science publication. Each year the Program Editorial Committee of the Conference attempts to select a theme that highlights a scientific or regulatory issue that is relevant, engaging and thought-provoking for all of the tobacco science community to consider. This year, the committee has chosen "Building Science and Evidence in the Regulated Tobacco Landscape" for the symposium theme. The symposium covers changes in the gathering of data and the presentation of information as the industry changes from the traditional combustible setting to a reduced risk and noncombustible environment. Four distinguished speakers were invited to provide their unique insights into the importance of science to the entire industry as we move into a more regulated climate in the United States. This publication contains the synopses of the symposium presentations and introductory remarks that include a brief biographical sketch of the symposium speakers. Members of the Program Editorial Committee, Summer Hanna, Jason Flora and I, wish to express our sincere appreciation to the speakers, Drs. Matt Holman, Katherine Ciambrone, Jason Flora, and Gene Gillman and their colleagues for the significant time and effort spent preparing the publications and presentations.

Kathy Humphries
Chair, Program Editorial Committee
72nd Tobacco Science Research Conference

INTRODUCTION TO THE SYMPOSIUM

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Since the passage of the Family Smoking Prevention and Tobacco Control Act in 2009, the US tobacco industry has undergone a shift from limited product regulation to a highly regulated industry. During this transition, the industry and the agency have proceeded down a path that has included product registrations, Substantial Equivalence applications, Pre-Market Tobacco Applications and finally the emergence of potential Modified Risk Tobacco Products. As we all venture into the regulation of newly deemed products, including e-cigarette and cigars, we now face even more challenges. There are many questions that remain to be answered:

- How do we gather the evidence and report the science generated in this evolving landscape of tobacco science?
- What are some of the approaches that have been taken to develop new products and what roles do these novel products play in harm reduction?
- How do we repair past missteps by the industry and rebuild trust among all stakeholders?

Clearly, navigating the diverse and dynamic world of science and industry and regulator relationships is complicated. The Symposium, comprised of presenters from the regulating body, two manufacturers and a contract laboratory, represents the multiple facets of this complex association. The symposium topic, "Building Science and Evidence in the Regulated Tobacco Landscape," was chosen by the Program Editorial Committee to present various means the industry and the FDA has undertaken to attempt to facilitate knowledge transfer and address these important questions faced by all stakeholders.

Matthew R. Holman, Ph.D. is currently Director of the Office of Science at the Center for Tobacco Products (CTP) of the U.S. Food and Drug Administration (FDA). He was appointed to this position in January 2017. The Office of Science at CTP is responsible for identifying, developing, and enhancing the science related to tobacco products, their use, and the resulting morbidity and mortality so that regulatory decisions will have the greatest impact on improving public health. To accomplish this goal, they provide the scientific support for regulations and guidance, review tobacco product applications, evaluate the knowledge basis for regulatory decisions, and carry out research to fill the gaps in scientific knowledge related to tobacco product regulation. He received his Ph.D. in Biochemistry

from the University of Maryland at College Park in 2000. Prior to taking his current position, Dr. Holman served as Director of the Division of Product Science within CTP's Office of Science for six years. In this position, he oversaw evaluation of the composition and design of tobacco products. In addition, he was involved in chemical, microbiological, and engineering research on tobacco products, resulting in numerous publications in peer-reviewed scientific journals. During this time, Dr. Holman also served as Technical Project Lead (TPL) in reviewing over a thousand SE Reports. As TPL, he was responsible for the overall scientific review of SE Reports by CTP. Before his tenure at CTP, he worked in FDA's Center for Drug Evaluation and Research (CDER) on over-the-counter drug products. He served in a few positions within CDER, with his last position being Deputy Director of the Division of Non-prescription Regulation Development. In this role, he was involved in the publication of approximately 50 rulemakings, guidance documents, and other Federal Register notices. He will begin the Symposium with a talk entitled "Importance of Science to FDA's Center for Tobacco Products."

Katherine Ciambrone, Senior Vice President and Chief Compliance Officer for ITG Brands, follows with a paper entitled "A Risk-based Approach to Tobacco Product Development & Control ." Katherine is accountable for the strategic direction and management of ITG Brands' Product Development & Science, Regulatory Affairs and Compliance programs. This includes preparing international sites for FDA Center for Tobacco Products new site manufacturing standards, as well as delivering and defending product registration and submissions as required by the Tobacco Control Act and subsequent Deeming regulations. Prior to joining ITG Brands, Katherine was in the pharmaceutical industry for over 25 years in various operational, compliance and risk management roles across R&D and Corporate functions. She holds a MS in Organizational Dynamics from the University of Pennsylvania and a MS in Quality Assurance & Regulatory Affairs from Temple University.

Jason W. Flora is currently a Senior Principal Scientist in the Scientific Strategy and Analysis group, a part of Altria Client Services (ALCS) in Richmond, Va. In this role, he conducts Regulatory Affairs Science Integration for Philip Morris USA and NuMark with a focus on the scientific substantiation and regulatory requirements for potentially reduced harm tobacco products. Over the last 16 years, Dr. Flora has held a variety of positions within the Altria family of companies. Most recently, he served as Senior Manager in the Sensory and Analytical Sciences group, where he led two teams of analytical scientists focusing on constituent analysis supporting analytical chemistry method development for regulatory reporting as well as new product investigations supporting various product development objectives. He has also held positions in the Health Science Research and has worked in the External Scientific Communications group.

Dr. Flora has a Ph.D. in analytical chemistry from Virginia Commonwealth University and serves as an adjunct faculty member at Virginia Commonwealth University teaching a graduate level Chemistry course focused on the theory and operation of analytical chemistry instrumentation. Dr. Flora's presentation is entitled "The Role of Non-combusted Products in Tobacco Harm Reduction."

The final presentation of the Symposium will be made by Dr. Gene Gillman, Sr. Vice-President of Tobacco Services at Enthalpy Analytical LLC. Dr. Gillman is the leader of Enthalpy, a CRO specializing in qualitative and quantitative analyses of compounds in tobacco, tobacco smoke, and electronic cigarettes. Dr. Gillman holds a Ph.D. in organic chemistry, with an emphasis on chemical toxicology, from Wake Forest University. He has spent his professional career investigating the constituents and chemistry of tobacco smoke. Dr. Gillman is also actively involved in the tobacco industry and is currently active on the US ISO TAG to TC 126 and serves as the Secretary of the CORESTA E-Vapour Subgroup. He will speak about how regulation has impacted contract research organization in his presentation, "The Impact of FDA regulation, a CROs perspective on changes in the industry."

Following the presentations, the symposium will conclude with an open panel discussion. All of the speakers will be invited back to the stage where they will field questions related to science and evidence generation. We encourage attendees to make the best use of the speakers' collective wealth of expertise and knowledge in this area and to actively participate in this question and answer session.
The Editorial Committee would like to recognize the speakers and organisations for their contributions to the symposium and extend our gratitude for their participation. We hope that the symposium is found to be informative, insightful and inspiring to conference participants and that the topics presented in the symposium will provide answers to some of the questions arising from the ever-changing landscape of tobacco science.

Kathy Humphries
72nd TSRC Symposium Chair

A RISK-BASED APPROACH TO TOBACCO PRODUCT DEVELOPMENT & CONTROL

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Abstract:
The Tobacco Industry does not appear to have a model that identifies those attributes of a product's characteristics and manufacturing processes having the greatest impact on a finished tobacco product's quality and compliance. As a result, regulators seem to consider all attributes of a tobacco product with the same criticality. This presentation proposes that a flexible regulatory framework for tobacco products could be achieved by utilizing a risk-based end-to-end control strategy similar to that established in the pharmaceutical industry. A control strategy is the description of the product, manufacturing process, facilities and equipment, and assurance elements that provides confidence in the consistency and quality of a product.

The first step of this approach is to clearly define the adult consumer's expectations of quality for a product's intended use. Only after that is defined, can a risk-based approach to tobacco product development and delivery enable a fit-for-purpose control strategy commensurate to expected quality, complexity and required compliance. An effective control strategy identifies product characteristics that are critical to meeting these predefined expectations. These critical characteristics are then evaluated by assessing the extent to which their variation can have negative impact on the finished tobacco product. Proportional controls are then designed in order to achieve the quality as defined in the first step. Once controls are identified and established, those critical attributes, or the process controls, should then be monitored to ensure that the product is consistently meeting quality and compliance expectations.

Using a risk-based approach ensures that the quality for intended use, product characteristics and manufacturing and supply chain complexity is considered in order to differentiate between simple products that may only require end-product testing and complex products that may require in-process controls and more release testing. It should be noted that a control strategy, for any tobacco product, should reflect of the level of maturity and effectiveness of the quality management system in place. As in the pharmaceutical industry, it should also be recognized that the quality of knowledge gained and provided to a regulatory agency, and not the quantity of data, should be the basis for regulatory evaluation.

Ultimately, a well-articulated and executed control strategy can consistently deliver the intended quality and compliance of a tobacco product. This approach should be considered as part of a reasonable regulatory framework that provides value for the adult consumers by ensuring consistent quality while providing options and access to new harm reduction products by reducing regulatory burden and cycle times.

This proposal is based on International Standards on Harmonization (ICH) Quality Guidelines (Q8, Q9 & Q10).

References:

- PHARMACEUTICAL DEVELOPMENT Q8(R2) Current Step 4 version dated August 2009
- QUALITY RISK MANAGEMENT Q9 Current Step 4 version dated 9 November 2005
- PHARMACEUTICAL QUALITY SYSTEM Q10 Current Step 4 version dated 4 June 2008

Introduction:

Other manufacturing industries utilize published models to differentiate between those product's characteristics having the greatest impact on quality and compliance and those characteristics that do not.

Examples of these models are the FDA CDRH's 510(k) premarket review program from medical devices and the pharmaceutical industry's Q8, Q9 and Q10 Guidelines as issued by the International Conference on Harmonization (ICH). Absent an agreed and transparent approach, tobacco regulators and industry take widely different approaches in determining which characteristics are most critical to a tobacco product's quality, compliance and considerations on the impact on public health. The lack of a standardized approach results in a loss of time, reputation and resources, for both regulators and industry, ultimately resulting in a diminished ability to prioritize the review of tobacco products that truly raise different questions of public health.

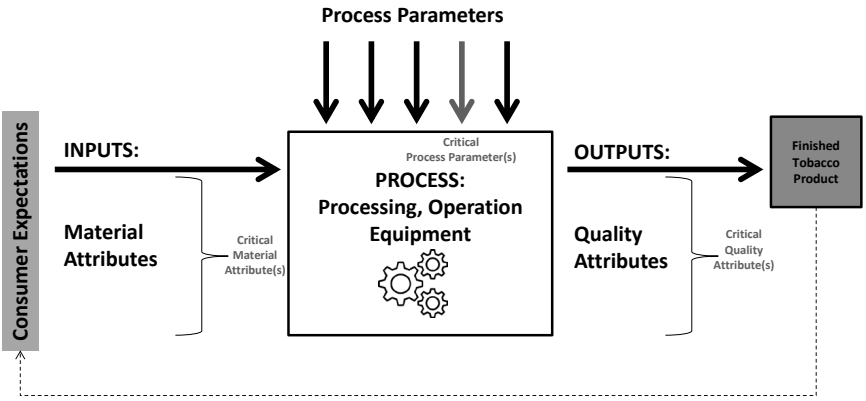
Recently, Dr. Scott Gottlieb, FDA Commissioner stated "I have asked CTP to consider whether its current plan, which is to review all of the so-called Provisional Substantial Equivalence products, is an effective use of its resources and whether it should continue to pursue the current approach to these reviews. I have asked CTP to consider whether there is an approach that makes more sense, and whether by not reviewing some of those products, those review resources could be freed up for other purposes and greater clarity could be provided to the market."

This paper proposes that a risk-based tobacco product development and control model, similar to ICH Quality approach, could be applied across all tobacco

products in order to achieve a similar flexible regulatory framework and therefore help achieve the FDA Commissioner's overarching intent.

Risk-based Control Strategy Overview:
A control strategy is a description of the product, manufacturing process, facilities and equipment, and assurance elements that provides confidence that a product meets standards for identity and quality. In order to establish an effective risk-based control strategy for tobacco products, it is critical to first ensure the requirements are clearly understood and defined. This can be achieved through a thorough understanding of the regulations impacting the product and by clearly identifying those attributes of a finished tobacco product that have the greatest chance of presenting different questions of public health. Through the product design and development process, the most important attributes which may impact questions of public health would be identified as Critical Quality Attributes (CQA). These CQAs, along with consumer acceptability criteria (i.e. consistency of product), would be the basis of a product's final acceptance criteria. Only after this baseline understanding is achieved, can a risk-based control strategy be developed that is commensurate with the expected quality and complexity of the product. A fit-for-purpose, risk-based control strategy helps narrow the focus to those product's characteristics that are critical to meeting those CQAs. Once these critical characteristics are identified, they can be evaluated to assess to what extent any variation, introduced throughout the manufacturing process, may cause a material impact on final product identity and quality. The overall impact of any variation is determined by the relationship between the material inputs and the manufacturing process. This relationship can be described as a product's design space. Once the impact of variation is understood, proportional controls should be designed and monitored throughout the manufacturing process in order to consistently achieve quality expectations.

Figure 1: Illustration of the relationship between Material Attributes, Process Parameters & Quality Attributes



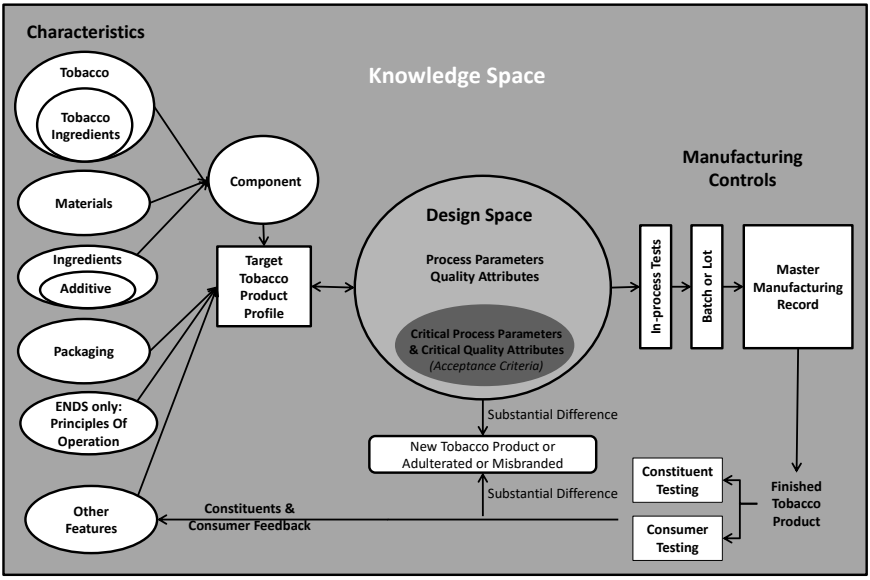
An effective risk-based control strategy ensures the quality for intended use, product characteristics, manufacturing process, supply chain complexity and maturity of a manufacturer's quality management system are all considered and addressed adequately. These considerations help differentiate between simple products that may only require visual end-product inspection and complex products that may require in-process or post-process controls.

Determining appropriate controls for Hand-rolled Cigars, as compared to Electronic Nicotine Delivery Systems, provides a good example of how a risk-based approach for tobacco products might be applied. A hand-rolled cigar has innate variability of 'input' materials based on limited controls on cigar tobacco seed, variable leaf growing conditions and supply. In addition, the manufacturing 'process' is not machine controlled and the 'output' is in extremely small batches. That combination of inherent variability should provide the rationale that Hand-rolled Cigars have a fundamentally different control strategy than an ENDS product. ENDS products are machine manufactured, have tobacco derived components usually interacting with an integrated heat-source, and are usually produced in large batch sizes that all must meet the same detailed specifications for release in order to ensure the quality of the product. In addition, many ENDS products can deliver different quantities of liquid based on modifiable device operations.

A well-defined risk-based control strategy that consistently delivers the intended quality and compliance of a product should be considered as a basis for reasonable regulations and product registration. As in the pharmaceutical industry, it should also be recognized that the quality of product knowledge provided to a regulatory agency, and not the quantity of data, should be the basis for regulatory evaluation.

Defining a Risk-Based Control Strategy for Tobacco Products:
After defining the CQAs, a risk-based control strategy would be integrated into the development stages of the product. Product design would be captured in a comprehensive and systematic manner and include any requirement to which a finished or in-process tobacco product or manufacturing process must conform. In this proposal, that record would be described as a Target Tobacco Product Profile (TTPP). The aim of tobacco product development is to design quality into the product's manufacturing process in order to consistently deliver to the adult consumer expectations on a batch-to-batch basis. The information and knowledge gained from product development studies and manufacturing experience provides the knowledge and information required in the TTPP and is the foundation of an effective risk-based control strategy.

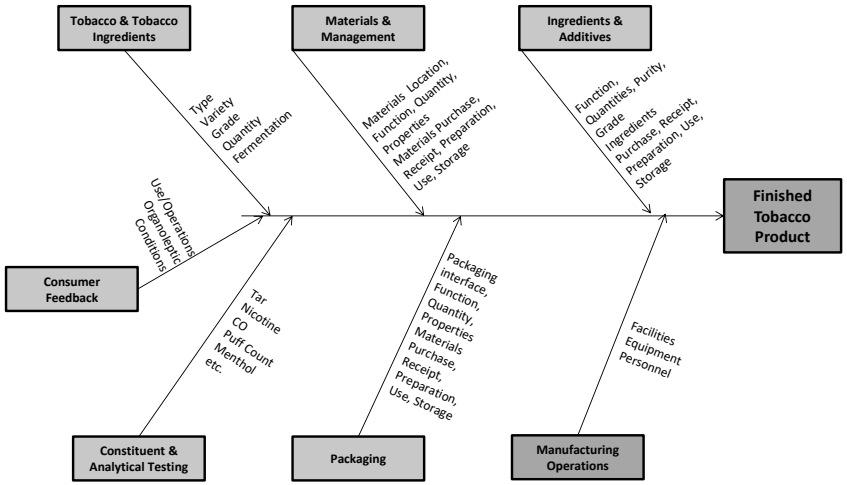
Figure 2: Tobacco Product Control Strategy



Attribute: Materials, Characteristics, Components, Constituents
Parameter: Process, Operations, Equipment settings

Product development studies should identify, at a minimum, those aspects of a tobacco product's attributes and manufacturing processes that are critical to ensuring the Finished Tobacco Product's CQAs. An evaluation of potential variables which could have an impact on desired quality would be conducted to identify critical attributes and parameters. Understanding sources of variability and their impact on downstream processes or processing, in-process materials, and product quality can provide an opportunity to shift controls upstream and minimize the need for retrospective testing. If implemented effectively, a Quality Management System for Good Manufacturing Practices, as proposed by the industry in 2012 in support of the FDA's Tobacco Control Act, Section 906(e), would be used to demonstrate controlled acceptable variability while also preventing contamination or adulteration of tobacco products. A ranking of the impact of those variables based on probability, severity or detectability using tools such as Fishbone or Failure Mode Effects Analysis (FMEA) or similar tools should be conducted based on historical knowledge and initial product development and manufacturing data.

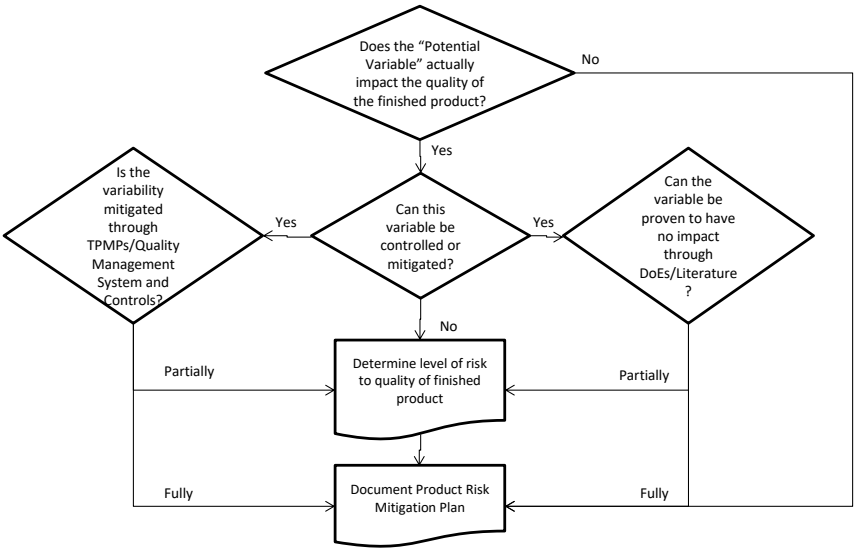
Figure 3: Example of the use of a Fishbone tool used to facilitate the identification of variables that could impact final product quality.



Attribute: Component, Characteristics
Parameter: Process, operation, equipment

A manufacturer could choose to conduct additional product development studies to enhance knowledge of the tobacco product's design space over a wider range of material attributes, processing options and process parameters.

Figure 4: Example: Use of a Decision Tree in determining the impact on variability.



To provide flexibility for future process improvement, a manufacturer could describe the manufacturing and measurement systems used to monitor critical attributes or process parameters. Through the collection of process monitoring data during the development of the manufacturing process applicants could provide useful information to enhance process understanding. The process control strategies that allow adjustment (manual or automated) capabilities while conducting in-process monitoring of critical attributes would be described to demonstrate rigor while moving within the acceptable range of the design space.

An assessment of the ability of the process to reliably produce a product of the intended quality (*e.g.*, the performance of the manufacturing process under different operating conditions, at different scales, or with different equipment) can be provided. An understanding of process robustness can be useful in risk assessment and risk reduction and to support future manufacturing and process improvement, especially in conjunction with the use of risk management tools.

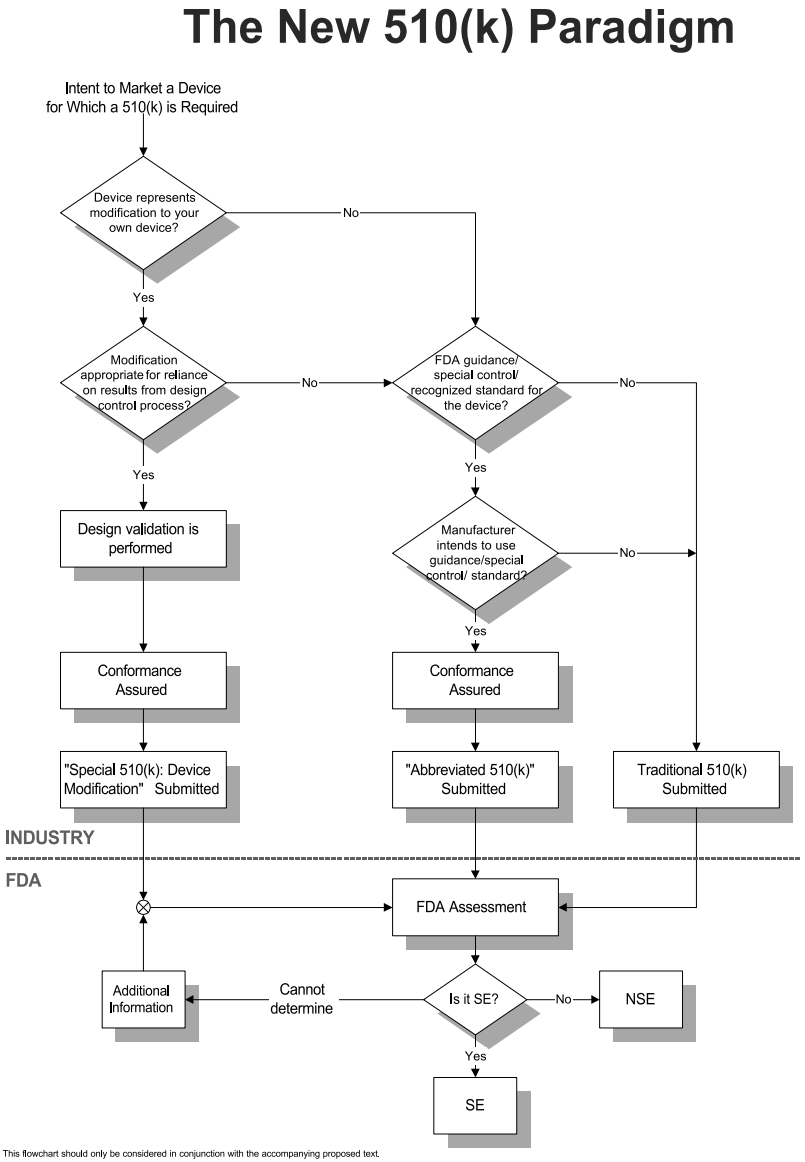
This broader understanding facilitates the establishment of an expanded design space, such as acceptable ranges for product release criteria, and would not ultimately impact the quality or compliance of the finished product and thus provides the foundation for a flexible regulatory framework. The inclusion of this additional information in regulatory applications should provide an opportunity to demonstrate a higher degree of understanding of material attributes, manufacturing processes and their controls and related impact on product quality and compliance. Throughout the product lifecycle, companies should have the opportunity to evaluate innovative approaches to improve product quality. Process performance can be monitored to ensure that it is working as anticipated to deliver product quality attributes as predicted by the design space. This approach embeds manufacturers with the responsibility to initially determine whether a particular modification requires a premarket review (905(j)) submission, with such "no requirement to file" determination subject to later inspection both during an application process or post approval.

An effective and strategic risk-based control strategy could be similarly applied to prospective changes to tobacco products that may normally be routed through a minor modification if a similarly agreed Regulatory Change Assessment checklist or decision tree was issued under FDA TCA Section 905(j)(3). This combination of Design Space, GMPs and a Risk-based Control Strategy could be used in combination for non-critical changes that are not likely to raise different questions of public health:

- for those changes intended to maintain batch-to-batch consistency (transitory adjustments that are not intended to permanently alter product characteristics)
- changes that are not likely to raise different questions of public health or product changes that decrease or eliminate an additive

- changes that reduce or maintain current levels of HPHCs and TNCOs
- changes in "commodity" ingredients (i.e., use of an interchangeable ingredient that meets a predefined specification/tolerance in use for the tobacco product)

Figure 5: Example: Decision Tree for deciding when to submit a 510(k) for a change to an existing device



Certain changes should be exempt from requiring such prior approval but would be subject to inspection, such as:

- changes mandated by law (*e.g.*, FSC Paper, changes intended to comply with a tobacco product standard)
- changes implemented by third-party vendors that do not impact the manufacturer's release specifications for the tobacco product at issue

The risk-based control strategy and design space is proposed by the tobacco manufacturer and would be subject to post-hoc regulatory assessment and approval. Working within the design space would not be considered as a change requiring premarket oversight by FDA. Individual product test data showing that individual test articles fell outside of specifications should not result in a determination that new tobacco products are NSE but are determined Out-of-Specification and investigated for root cause and mediated in accordance with applicable GMP requirements. Changes that permanently move the product out of the design space, or outside the agreed parameters of the decision trees, would be considered to be a change and should presumptively initiate a regulatory premarket review process as that would be considered a new tobacco product. Akin to FDA CDRH's 510(k) program, manufacturer use of decision-tree, and a determination that no regulatory filing is required in connection with a particular change or changes, would be adequately documented and made available to FDA in connection with a later inspection, and would be subject to enforcement if FDA disagrees with the manufacturer's rationale and decision.

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THE ROLE OF NON-COMBUSTED PRODUCTS IN TOBACCO HARM REDUCTION

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Abstract
Today, FDA has regulatory authority over all tobacco products. FDA acknowledges that there is a continuum of risk for tobacco products and distinguishes between the harm associated with combustible versus non-combustible products. A harm-reduction strategy that informs adult smokers about reduced-risk products, subject to FDA oversight, will complement, not compete, with proven prevention and cessation strategies. This approach should focus on reducing tobacco-related morbidity and mortality among the population of adults who continue to use tobacco products by empowering them to make an informed decision to choose a product proven to be lower on the continuum of risk. That is why we invest in developing a portfolio of non-combustible tobacco products. We've been concentrating on three product platforms. These include smokeless and other oral nicotine containing products, e-vapor, and heated tobacco products. We believe adult smokers unable or unwilling to quit are more likely to completely switch from cigarettes if they can choose from a variety of acceptable alternative tobacco products. Of course, we can only compete in the marketplace with products authorized by the FDA and we can only communicate reduced harm or risk claims if FDA grants authorization to a Modified Risk Tobacco Product Application (MRTPA). As manufacturers, it is critical to develop a variety of innovative reduced harm tobacco products that are acceptable alternatives to conventional cigarettes for adult smokers, transparently provide extensive science and evidence about these products, and, with FDA authorization, bring them to market. FDA and the broader public health must provide reasonable regulatory pathways, unbiased scientific assessments, collaborative research, and science and evidence based differential risk communications about these products. A diverse market of FDA-authorized, non-combustible products with accompanying modified risk claims will enable informed decisions for adult cigarette consumers to choose products proven to be lower on the continuum of risk and thus is an extremely important step in advancing tobacco harm reduction in the U.S.

Introduction
Cigarette smoking is the leading cause of preventable death and disease in the United States. The 2010 U.S. Surgeon General report noted that "Inhaling the complex chemical mixture of combustion compounds in tobacco smoke causes adverse health outcomes, particularly cancer, cardiovascular and pulmonary diseases, through mechanisms that include DNA damage, inflammation, and

oxidative stress." (1) Eliminating or significantly reducing levels of harmful and potentially harmful constituents (HPHCs) present in conventional cigarette smoke has long been recognized as a promising avenue for reducing the toxicity and health risks of tobacco products when compared to conventional cigarettes. For example, in 2001, the U.S. Institute of Medicine (IOM) stated, "[f]or many diseases attributable to tobacco use, reducing risk of disease by reducing exposure to tobacco toxicants is biologically and clinically feasible" (2).

Despite efforts to persuade people never to start or to quit if they do, millions of adults will continue using tobacco products. For these consumers, reduced-risk products may offer a promising opportunity to reduce the harm associated with tobacco use, particularly cigarette smoking. A strong public health consensus has formed that not all tobacco products present the same risk. Public health authorities agree that there is a broad continuum of risk among tobacco products, with conventional cigarettes at the highest end of that spectrum. This continuum recognizes that most of the harm caused by tobacco results from the burning of tobacco (3-7).

Today, FDA has regulatory authority over all tobacco products. FDA acknowledges the continuum of risk for tobacco products and distinguishes between the harm associated with combustible versus non-combustible products. For example, as part of the July 28, 2017 announcement, the FDA commissioner Dr. Scott Gottlieb acknowledged a continuum of risk among tobacco products, with conventional, combustible cigarettes at the highest end of that spectrum and non-combustible products on the lower end. He also stated that "[W]e must also take a new and fresh look at the noncombustible side" (8). In a 2009 publication titled "The Strategic Dialogue on Tobacco Harm Reduction: a vision and blueprint for action in the US," Zeller *et al*. reached the following consensus: "On the continuum of risk, non-combustible tobacco products are more likely to reduce harm than a smoked form of tobacco for individuals who would otherwise be using conventional cigarettes" (9). Additionally, the Royal College of Physicians in London stated in 2002 that "[T]he consumption of non-combustible tobacco is of the order of 10-1,000 times less hazardous than smoking, depending on the product" (10).

A harm-reduction strategy that informs adult smokers about reduced-risk products, subject to FDA oversight, will complement, not compete, with proven prevention and cessation strategies. This approach should focus on reducing tobacco-related morbidity and mortality among the population of adults who

continue to use tobacco products by empowering them to make an informed decision to choose a product proven to be lower on the continuum of risk.

There are currently about 40 million adult cigarette smokers in the U.S. According to data from the FDA's Population Assessment of Tobacco and Health (PATH) study, more than half, or 22 million, of these smokers are interested in satisfying but less harmful nicotine alternatives to conventional cigarettes (11). That is why we invest in developing a portfolio of non-combustible tobacco products that adult smokers enjoy, while conducting the necessary science to bring them to market. A portfolio approach is important because we know that not all smokers are looking for the same experience. We've been concentrating on three product platforms. These include smokeless and other oral nicotine containing products, e-vapor, and heated tobacco products. We believe adult smokers unable or unwilling to quit are more likely to completely switch from cigarettes if they can choose from a variety of acceptable alternative tobacco products. Of course, we can only compete in the marketplace with products authorized by the FDA and we can only communicate reduced harm or risk claims if FDA grants authorization through the Modified Risk Tobacco Product Application (MRTPA) requirements set forth by the sections 911 of the 2009 Family Smoking Prevention and Tobacco Control Act (12-13).

Pursuant to the statute and FDA guidance, a MRTPA should include a substantial amount of information including packaging and labeling, proposed health claims, product design, manufacturing procedures, quality control measures, chemistry and physical characterization, toxicology and risk assessments, clinical studies, perception and behavior assessments, populations modeling, and post-market surveillance plans (12-13). It is not only important to demonstrate that the new candidate product reduces exposure and risk of tobacco-related disease, but also show that the product does not interfere with cessation and does not appeal to non-tobacco users. FDA will consider the totality of the evidence provided in the applications and allow marketing of the MRTP if the scientific evidence sufficiently demonstrates that the product, as it is actually used by consumers, will "significantly reduce harm and the risk of tobacco-related disease to individual tobacco users; and 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." (12-13)

We have established a rigorous scientific framework to evaluate potentially reduced-harm tobacco products based on FDA's guidance and approaches recommended by members of public health (2-4,12-14). However, the body of scientific evidence that should be provided in a MRTPA can vary between product platforms. For example, while promising scientific evidence exists in support of e-vapor and heated tobacco products as potential MRTPs compared to conventional cigarettes, long-term exposure data are limited. Thus, extrapolations must be made regarding

long-term exposure based upon the totality of scientific evidence available (*e.g.*, chemistry data, toxicological assessments, and clinical studies). Conversely, tobacco products that have been used by adult consumers for many decades, such as traditional smokeless tobacco (ST) products, have epidemiological data that can be relied upon to assess the effects of long-term exposure.

Smokeless Tobacco

A vast body of epidemiology on ST products demonstrates that such products present significantly lower risk than conventional cigarettes. Adult smokers who are unwilling or unable to quit smoking should be encouraged to switch to a less harmful product, like ST products. Notwithstanding efforts by government, public health and others to encourage them to quit, millions of adults are likely to continue using tobacco products, including a considerable number of adult ST consumers who continue to smoke. In the U.S., there are approximately 6.6 million adult ST users, of which 2.3 million also smoke and are referred to as "dual users." (11) Dual users present a significant harm-reduction opportunity because, having already made the choice to use ST, they may be more open to using ST exclusively and giving up cigarettes entirely.

Many adult tobacco consumers wrongly believe that ST products are as harmful as conventional cigarettes, or even more harmful. For example, in the PATH Wave 1 survey, the vast majority of smokers (more than 90%) said that ST is as or more harmful than cigarettes (11). Similar findings are evident in the HINTS (Health Information National Trends) survey where a vast majority of smokers (71%) and dual users (72%) did not believe that ST is less harmful than cigarettes (ALCS analysis of the 2015 National Cancer Institute Health Information National Trends Survey) (15). Numerous published studies corroborate these findings (16-19).

ST products are not safe. The overwhelming scientific, medical, and public health consensus, however, confirms that ST products, including those widely available in the U.S., are substantially less hazardous than conventional cigarettes (9,20). This consensus is based on extensive and compelling scientific evidence, including epidemiological disease risk data in human populations from the U.S.

Many global public health organizations accept the scientific fact that ST is far less hazardous than cigarette smoking. For example:

> "[U]sers of smokeless tobacco products generally have lower risks for tobacco-related morbidity and mortality than users of combustible tobacco products such as cigarettes" (21).
>
> "Overall therefore, in relation to the risks of the above major smoking-related diseases, and with the exception of use in pregnancy, [smokeless

> tobacco products] are clearly less hazardous, and in relation to respiratory and cardiovascular disease substantially less hazardous, than cigarette smoking" (22).

Published epidemiology and our analyses of two nationally representative public health surveys linked to the National Death Index (NHIS and NLMS data sets for ST users and cigarette smokers compared to never tobacco use) (23-25) clearly show that completely switching from cigarettes to ST products presents significantly lower overall health risks than cigarettes. The epidemiological evidence is the foundation of the U.S. Smokeless Tobacco Co. MRTPA submitted for Copenhagen® Snuff on March 20, 2018.

Heated Tobacco Product - iQOS

We are actively supporting Philip Morris International's (PMI) efforts to bring to market a new heated tobacco product called iQOS. The iQOS tobacco heating system (THS) is an important step forward in providing tobacco enjoyment to adult tobacco consumers with the potential for less risk. For those U.S. adult smokers seeking an alternative to conventional cigarettes, iQOS will offer a great sensory experience with similar nicotine satisfaction in a familiar format, using real tobacco, but with no ash and less lingering odor. And at the same time, PMI's extensive regulatory filings for iQOS present a compelling case for the product's harm reduction potential. If authorized by the FDA, Philip Morris USA will sell iQOS in the U.S. Some of the key scientific findings are discussed below. Because the scientific assessments for iQOS have been extensive and cover a range of disciplines (*i.e.*, chemistry, toxicology, clinical studies, perception and behavior, post-market studies), this discussion is not intended to cover all aspects of the scientific evaluations. An overview of the chemistry and clinical data will be provided.

The iQOS THS is a non-combustible tobacco product that heats and does not burn the tobacco. The highest observed temperature of the tobacco in the Tobacco Stick when used with the iQOS system is approximately 300°C and cannot exceed 350°C. In conventional cigarettes, temperatures reach up to 900°C where both pyrogenesis and pyrosynthesis of HPHCs occurs from the thermal decomposition of the organic compounds that are present in the tobacco (26-27). Therefore, a reduction of toxicants can be achieved by heating the tobacco rather than burning it as clearly demonstrated by the compelling scientific evidence provided in PMI's pre-market tobacco applications (PMTAs) and MRTPAs for iQOS.

iQOS is a new tobacco product, and epidemiological data are not available. The chemistry, toxicology, and clinical data, however, are extremely promising. Extensive research demonstrates that iQOS reduces levels of HPHCs, other than nicotine, by more than 90% compared to conventional cigarettes (27). As a result

of the reduced HPHCs in the aerosol of iQOS, as compared to conventional cigarettes, favorable outcomes are observed in numerous toxicological assessments (*in vitro* and *in vivo*) (27). Meaningful reductions in biomarkers of exposure and biomarkers of potential harm are also observed in smokers who switch to this non-combusted tobacco product as demonstrated through multiple clinical studies (28,29).

The reduced HPHCs in iQOS have also been confirmed by independent researchers. For example, in a recent 2018 publication by Mallock *et al.*, in Archives of Toxicology, the authors state that "Our study confirms that levels of major carcinogens are markedly reduced in the emissions of the analyzed HNB [heat-not-burn] product in relation to the conventional tobacco cigarettes and that monitoring these emissions using standardized machine smoking procedures generates reliable and reproducible data which provide a useful basis to assess exposure and human health risks" (30).

PMI submitted MRTPAs for iQOS in December 2016 and PMTAs in March 2017. FDA is currently evaluating the scientific evidence in these applications, and select results from scientific studies will be shared in the presentation.

E-Vapor Products

E-vapor products, often referred to as electronic cigarettes, e-cigarettes, or Electronic Nicotine Delivery Systems (ENDS), are battery-operated, tobacco-derived nicotine products that generate aerosols by heating liquid formulations (e-liquids) consisting primarily of propylene glycol (PG), glycerin (or vegetable glycerin (VG)), nicotine, and flavors. E-vapor products have gained considerable popularity in the world-wide marketplace and have shown to be acceptable alternatives to many adult tobacco consumers. E-vapor products are available in a variety of configurations including small devices resembling cigarettes that are disposable or have rechargeable batteries with disposable (or consumable) cartridges (referred to as "cig-a-likes") or larger formats with rechargeable batteries and disposable prefilled or refillable tanks.

Like iQOS, long-term epidemiological data are not available for e-vapor products; however, the scientific evidence is also extremely promising. Because the scientific assessments of e-vapor products have been extensive and cover a range of disciplines (*i.e.*, chemistry, toxicology, clinical studies, perception and behavior, post-market studies), this discussion is not intended to cover all aspects of the scientific evaluations. An overview of our chemistry and clinical analysis will be discussed.

Heating the known mixtures of liquid instead of burning tobacco prevents the generation of many of the HPHCs found in conventional cigarette smoke, and

the HPHCs that are present, other than nicotine, are typically reduced by more than 95% or not even detectable when compared to cigarette smoke (31). Adult smokers who completely switch to exclusive use of the these products are typically exposed to fewer and significantly lower levels of HPHCs and exhibit significant reductions of selected biomarkers of exposure, and favorable changes in selected biomarkers of potential harm, when compared to adult smokers who continue to smoke conventional cigarettes.

Members of the public health community are increasingly recognizing the potential of e-vapor products and their role in tobacco harm reduction. For example, in a 2016 report by the Royal College of Physicians, "Nicotine without smoke, Tobacco harm reduction," it is stated that "Although it is not possible to quantify the long-term health risks associated with e-cigarettes precisely, the available data suggest that they are unlikely to exceed 5% of those associated with smoked tobacco products, and may well be substantially lower than this figure" (32). Additionally, in the U.S., the American Cancer Society published in its website their position on e-cigarettes in February 2018. They stated that "Some smokers, despite firm clinician advice, will not attempt to quit smoking cigarettes and will not use FDA approved cessation mediations." They also stated that "These individuals should be encouraged to switch to the least harmful form of tobacco product possible; switching to the exclusive use of e-cigarettes is preferable to continuing to smoke combustible products" (33).

Closing

Smoking rates are at an all-time low. There are still about 40 million adult cigarette smokers in the U.S. and more than half of these smokers are interested in satisfying but less harmful nicotine alternatives to conventional cigarettes (11). That is why we invest in developing a portfolio of non-combustible products that adult smokers enjoy, while conducting the necessary science to bring them to market. A portfolio approach is important because not all smokers are looking for the same experience.

PMTAs must be submitted when seeking authorization for new tobacco products. The objectives of the PMTAs are to demonstrate that the new products are "appropriate for the protection of public health" (12). MRTPAs and FDA authorization are required in order to communicate reduced harm/risk claims for non-combustible tobacco products. The objectives of the MRTPAs are to demonstrate that the tobacco product, as it is actually used by consumers, will "significantly reduce harm and risk of tobacco-related disease to individual users" and will "benefit the health of the population as a whole taking into account both users of the tobacco products and persons who do not currently use tobacco products" (12). The science and evidence necessary for a MRTPA is different for new products (*e.g.*, e-vapor and heated tobacco products) where decades of

exposure data do not exist compared to traditional products (*e.g.*, ST) where epidemiological data is available.

Tobacco manufacturers, FDA, and the broader public health community have a role to play in continuing the advancement of tobacco harm reduction. As manufacturers, it is critical to develop a variety of innovative reduced harm tobacco products that are acceptable alternatives to conventional cigarettes for adult smokers, transparently provide extensive science and evidence about these products, and, with FDA authorization, bring them to market. FDA and the broader public health must provide reasonable regulatory pathways, unbiased scientific assessments, collaborative research, and science and evidence based differential risk communications about these products. A diverse market of FDA-authorized, non-combustible products with accompanying modified risk claims will enable informed decisions for adult cigarette consumers to choose products proven to be lower on the continuum of risk and thus is an extremely important step in advancing tobacco harm reduction in the U.S.

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THE IMPACT OF FDA REGULATION, A CRO'S PERSPECTIVE ON CHANGES IN THE INDUSTRY

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Abstract
The signing of the Tobacco Control Act (TCA) on June 22, 2009 caused far reaching and permanent changes to the regulation and testing of tobacco products in the US. These changes have been seen in all aspects of the industry including manufacturing, labeling, product development and also analytical testing. The TCA created a framework for tobacco product regulation however, did not include details on how products would be regulated. The TCA also outlines a clear timeline for regulatory milestones from the submission of Substantial Equivalence (SE) applications to the establishment of the list of harmful and potentially harmful compounds in tobacco products. The agency has failed to meet many of these milestones and in turn granted extensions or enforcement discretion to the industry. The agency has also been delayed in the publication of rules and guidance documents related to regulatory submissions. These delays have presented a broad range of challenges to the industry and also to the organizations that service the industry including contract research laboratories (CROs). CROs are integral to the agency and the industry since they provide analytical testing services required for submission of product application. Since the passage of the TCA, CROs have prepared to meet the requirements of the FDA, often by trying to anticipate the requirements. Changes in FDA guidance has resulted in excess capacity or unneeded capabilities in the CROs. This presentation will focus on how CROs have responded to the challenges related to the changing regulatory landscape with a focus on the impact of changes and delays in tobacco product regulation guidance from the FDA.

Introduction
The fundamental business purpose of a tobacco contract research laboratory (CRO) in the tobacco industry has always been the analysis of samples on a fee for service basis. The tobacco CRO fills three main roles: 1) Provides routine analytical testing services to tobacco manufacturers, 2) provides analytical testing services to manufacturers and government researchers that might not have the resources to test tobacco products, and 3) provides an independent organization that can validate methods and verify results produced by other researchers. Defining "tobacco CROs" can be difficult, as it can include a wide range of laboratory services, including toxicology testing, bio-analytical testing, clinical trial studies and many others. Here, the scope will be limited to a laboratory that provides services related to the measurement and reporting of constituents in

tobacco, finished goods, and smoke. Further, this presentation will focus only on the impact of the Tobacco Control Act (TCA) on the CRO industry and changes from 2007 to the present.

Tobacco Control Act (2007 -2011)

The signing of the TCA on June 22, 2009 (1) caused far reaching and permanent changes to the regulation and testing of tobacco products in the US. These changes have been seen in all aspects of testing related to combustible products, smokeless tobacco and more recently electronic nicotine delivery systems. In order to understand the changes, it is necessary to review the industry prior to 2009. Before the passage of the tobacco control act, the primary role of the tobacco CRO was to support both product stewardship testing and product development activities. Regulatory testing, like annual CDC reporting or cigarette ignition propensity testing, was a small portion of total work prior to the TCA. With the passage of the TCA, the role of the CRO switched from one of discretionary product support to the new role of suppling data for product related regulatory filings, including Substantial Equivalence (SE) applications and PreMarket Tobacco Applications (PMTA). The TCA changed the US tobacco testing industry which in turn changed the tobacco CRO into a crucial resource for providing testing related to FDA regulation of the industry.

The transition that occurred in the CRO industry was driven by three main factors. Firstly, the TCA regulated the introduction of deemed products onto the US market. This was done through both the SE and PMTA approval process. These pathways were initially poorly defined in the TCA and until further guidance was issued in 2011, (2,3) it was not obvious to the industry how to comply with the FDA requirements. Secondly, it was clear in the TCA that a large amount of testing would be required to support all deemed products. However, exactly how and what testing would be required was unclear. Thirdly, the TCA required the disclosure of tobacco product details including tobacco and smoke constituents which discouraged some companies from engaging in product testing programs. This requirement may have indirectly lead to the approximately 25% decrease in routine product testing my laboratories saw in 2009 versus 2008. Text from Section 904 of the TCA is given below.

> "Each tobacco product manufacturer or importer, or agents thereof, shall submit to the Secretary the following information: … Beginning 6 months after the date of enactment of the Family Smoking Prevention and Tobacco Control Act, all documents developed after such date of enactment that relate to health, toxicological, behavioral, or physiologic effects of current or future tobacco products, their constituents (including smoke constituents), ingredients, components, and additives."

All of these factors lead to two changes in the CRO industry. The uncertainty around the testing requirements lead to a revenue decline, while at the same time capacity and capabilities were expanded to meet expected future testing needs. In 2009, there was concern that limited testing capacity would negatively impact the industry's ability to satisfy the FDA's future requirements. While there was no guidance in the TCA on what testing might be required, it was clear that the agency was concerned enough about testing capacity that it was mentioned several times in the TCA. The concern was great enough to warrant a provision in the TCA to extend the filing date for small manufactures if laboratory capacity was limited or not available in a timely manner. Text from Section 915 of the TCA is given below.

> "**Joint Laboratory Testing Services.** The Secretary shall allow any 2 or more small tobacco product manufacturers to join together to purchase laboratory testing services required by this section on a group basis in order to ensure that such manufacturers receive access to, and fair pricing of, such testing services.
>
> **Extensions for Limited Laboratory Capacity**
> **Conditions.** Notwithstanding the requirements of this section, the Secretary may delay the date by which a small tobacco product manufacturer must be in compliance with the testing and reporting required by this section until such time as the testing is reported if, not later than 90 days before the deadline for reporting in accordance with this section, a small tobacco product manufacturer provides evidence…
>
> **Extension.** The Secretary, taking into account the laboratory testing capacity that is available to tobacco product manufacturers, shall review and verify the evidence submitted by a small tobacco product manufacturer in accordance with paragraph (2). If the Secretary finds that the conditions described in such paragraph are met, the Secretary shall notify the small tobacco product manufacturer that the manufacturer shall not be considered to be in violation of the testing and reporting requirements of this section until the testing is reported or until 1 year after the reporting deadline has passed…."

This section of the TCA was taken by many to imply that testing required to support product applications would be extensive and exceed the capacity of the CRO industry. Many in the CRO industry expected the TCA would lead to a massive increase in total annual testing. These projections lead to capacity expansions at all CROs and also led to three new CROs expanding into the field of finished tobacco product testing. However, delays in FDA guidance actually led to a decrease in product testing in 2009 and 2010. SE guidance for cigarettes and

other deemed products was not issued until January of 2011 (1) while SE reports were due in March 2011 which led to the submission of many SE reports without any analytical testing to support the submission.

Harmful and Potentially Harmful Compounds (2010-2012)

Tobacco smoke is known to contain over 5000 compounds (4) but the number of compounds of regulatory concern has been historically limited to a much smaller subset of harmful or potentially harmful compounds (HPHCs) (5,6). Before the passage of the TCA, the industry routinely tested for approximately 50 compounds, many of which were included on the Health Canada regulatory reporting list (7). The number of compounds tested varied with the purpose of the testing, but typically included a wide range of compounds including VOCs, TSNAs, BaP and phenols. The TCA included a requirement for the FDA Center for Tobacco Products (CTP) to establish a new list of Harmful or Potentially Harmful compounds in both tobacco products and tobacco smoke. Text from Section 904 of the TCA is given below.

> "Not later than 24 months after the date of enactment of the Family Smoking Prevention and Tobacco Control Act, the Secretary shall establish, and periodically revise as appropriate, a list of harmful and potentially harmful constituents, including smoke constituents, to health in each tobacco product by brand and by quantity in each brand and subbrand. The Secretary shall publish a public notice requesting the submission by interested persons of scientific and other information concerning the harmful and potentially harmful constituents in tobacco products and tobacco smoke."

To meet this requirement, the FDA CTP commissioned a Tobacco Products Scientific Advisory Committee (TPSAC) to review the scientific literature and recommend the compounds for inclusion on the regulatory HPHC list. This TPSAC held several public meetings in 2010 and proposed recommended selection criteria to the FDA in August of 2010. In early 2011, the FDA published a draft of the HPHC compounds for public comment followed by publication of the list later in the year8. In the construction of the list, the agency took a wide view on which compounds to include. From the HPHC guidance document:

> "This guidance represents the Agency's current thinking on the meaning of the term "harmful and potentially harmful constituent" in the context of implementing section 904(e) of the FD&C Act. It states: "FDA believes that the phrase `harmful and potentially harmful constituent' includes any chemical or chemical compound in a tobacco product or in tobacco smoke: (a) That is or potentially is inhaled, ingested, or absorbed into the body; and (b) that causes or has the potential to cause direct or

> indirect harm to users or non-users of tobacco products". The HPHC final guidance includes examples of constituents that have the potential to cause direct harm and examples of constituents that have the potential to cause indirect harm:"

The FDA's selection criteria lead to the inclusion of several classes of compounds that were outside of the scope of routine tobacco laboratory testing. In addition to compounds on the Health Canada List, the new HPHC included an expanded list of VOCs, PAHs, nitrosamines, metals and aromatic amines and also new classes of compounds including dioxin/furans, radioisotopes and heterocyclic amines. This list is given in Table 1 along with compounds on the Health Canada Regulatory reporting list.

Table 1: Compounds on the FDA Cigarette Smoke HPHC List

Class	Compounds	Routine Methods-Pre-FDA
TNCO	Nicotine, Carbon Monoxide	Yes, Health Canada
Ammonia	Ammonia	Yes, Health Canada
Carbonyls	Acetone, Acetaldehyde, Acrolein, Butyraldehyde, Crotonaldehyde, Formaldehyde, Methyl ethyl ketone, Propionaldehyde	Yes, Health Canada
Phenols	Catechol, Cresols (o-, m-, and p-cresol), Phenol, Resorcinol	Yes, Health Canada
Volatiles	1,3-Butadiene, Acrylonitrile, Benzene, Isoprene, Toluene	Yes, Health Canada
Other Volatiles	Furan, Ethylene oxide, Vinyl chloride, Propylene oxide, Nitromethane, 2-Nitropropane, Vinyl Acetate	No
Semi Volatiles	Pyridine, Quinoline, Styrene	Yes, Health Canada
Semi Volatiles (other)	Ethylbenzene, Nitrobenzene, Acetamide, Acrylamide	No
HCN	Hydrogen cyanide	Yes, Health Canada
Nitrosamines (TSNAs)	4-(Methylnitrosamino)1-(3-pyridyl)-1butanone (NNK), N-Nitrosonornicotine (NNN)	Yes, Health Canada
Volatile Nitrosamines	N-Nitrosodimethylamine (NDMA), N-Nitrosopiperidine (NPIP), N-Nitrosopyrrolidine (NPYR), N-Nitrosodiethylamine (NDEA), N-Nitrosomethylethylamine	No
Nitrosamines (other)	N-Nitrosodiethanolamine (NDELA)	No

Polynuclear Aromatic Hydrocarbons (PAHs)	Benz[a]anthracene, , Benzo[b] fluoranthene, Benzo[c]Phenanthrene, Benzo[k]fluoranthene, Chrysene, Cyclopenta[c,d]pyrene, Dibenz[a,h]acridine, Dibenz[a,h] anthracene, Dibenz[a,j]acridine, Dibenzo[a,e]pyrene, Dibenzo[a,h] pyrene, Dibenzo[a,i]pyrene, 5-Methylchrysene,Dibenzo[a,l]pyrene, Indeno[1,2,3-cd]pyrene,	No
PAHs	Benzo[a]pyrene	Yes, Health Canada
Volatile PAHs	Naphthalene, Benzo[b]furan	No
Aromatic Amines	1-Aminonaphthalene, 2-Aminonaphthalene, 4-Aminobiphenyl,	Yes, Health Canada
Aromatic Amines	o-Anisidine, o-Toluidine, 2,6-Dimethylaniline	No
Heterocyclic Amines (Aza-arenes)	A-a-C (2-Amino-9Hpyrido[2,3-b] indole), Glu-P-1 (2-Amino-6methyldipyrido[1,2a:3',2'-d] imidazole), Glu-P-2 (2-Aminodipyrido[1,2a:3',2'-d] imidazole), IQ (2-Amino-3methylimidazo[4,5f]quinoline), MeA-a-C (2-Amino-3-methyl)9H-pyrido[2,3-b]indole), Trp-P-1 (3-Amino-1,4-dimethyl5H-pyrido[4,3-b]indole), Trp-P-2 (1-Methyl-3-amino-5Hpyrido[4,3-b] indole), PhIP	No
Metals	Arsenic, Cadmium, Chromium, Lead, Nickel, Selenium	Yes, Health Canada
Metals	Beryllium, Beryllium and Cobalt	No
Polonium 210	Polonium-210	No
Ethyl Carbamate (urethane)	Ethyl carbamate (urethane)	No
Chlorinated dioxins/furans	Chlorinated dioxins/furans	No
Caffeic acid	Caffeic acid	No
Hydrazine	Hydrazine	No

Publication of the HPHCs list led to a rapid and frantic expansion of testing capabilities in the CRO industry. From late 2010 to early 2012, new methods were developed and validated to cover the full 93 HPHC list. In order to bring these methods online in a relatively short time window, additional staff were hired, instrumentation was purchased, and physical space was added across the industry. By early 2012, at least three CROs had the required methods in place to test either all, or at least the majority of FDA 93 HPHC list.

Regulatory Reporting (2012)

The TCA included a provision that HPHCs would be reported to the agency and then communicated to the public in a meaningful manner. The CRO industry had prepared for regulatory compliance testing to support FDA application and also for routine testing of HPHCs in deemed tobacco products. CROs had added capacity and methods to be ready for the initial 2012 reporting deadline. Text from TCA sections 904 and 915 are given below.

> **Section 904**
>
> "Beginning 3 years after the date of enactment of the Family Smoking Prevention and Tobacco Control Act, a listing of all constituents, including smoke constituents as applicable, identified by the Secretary as harmful or potentially harmful to health in each tobacco product, and as applicable in the smoke of each tobacco product, by brand and by quantity in each brand and subbrand. Effective beginning 3 years after such date of enactment, the manufacturer, importer, or agent shall comply with regulations promulgated under section 915 in reporting information under this paragraph, where applicable"
>
> **Section 915**
>
> **"Testing, Reporting, and Disclosure.** Not later than 36 months after the date of enactment of the Family Smoking Prevention and Tobacco Control Act, the Secretary shall promulgate regulations under this Act that meet the requirements of subsection."
>
> "(The FDA) shall require testing and reporting of tobacco product constituents, ingredients, and additives, including smoke constituents, by brand and subbrand that the Secretary determines should be tested to protect the public health…"
>
> **"Subsequent and Additional Testing and Reporting.** The regulations promulgated under subsection (a) shall provide that, with respect to any subsequent or additional testing and reporting of tobacco products…"

As mentioned prior, testing was expected to exceed industry capacity and, in an attempt to meet demand, at least three new CROs had expanded into tobacco product testing. In order to be ready for 2012, all CROs had expanded to prepare for the expected rush of routine HPHC testing. However, due to lack of guidance from the agency on how to comply with the reporting requirements, few companies were prepared to engage in testing before guidance was issued by the FDA. The end result was that CROs used the extra time to continue to expand capacity with the expectation that FDA guidance would be forthcoming. In March of 2012, the agency issued guidance on reporting HPHCs in tobacco products and tobacco smoke that instead reduced the testing burden to only a subset of compounds. Compounds are shown in Table 2. The list is commonly known as the abbreviated HPHC 20 list. In part, lack of laboratory capacity was cited by the FDA as a reason to reduce the scope of the testing. Text from the 2012 guidance document:

> "We recognize that industry will have a short time between the establishment of the HPHC list and June 22, 2012 when the reporting obligations under section 904(a)(3) are effective. We also recognize that manufacturers or importers (particularly small tobacco product manufacturers may not currently have the in-house laboratory capabilities to test for quantities of HPHCs. Consequently, manufacturers or importers may rely on contract laboratories for HPHC testing. Because this will be the first time that tobacco product manufacturers or importers are required to report quantities of HPHCs, contract laboratories may not be prepared for the large volume of requests for the testing of quantities of the HPHCs for all brands and subbrands of tobacco products marketed prior to June 22, 2012."

To date, the FDA has only issued the 2012 HPHC guidance. Since 2012, there has not been a request from the agency for any routine HPHC reporting under Section 915 of the TCA or a revision of the abbreviated HPHC list. The HPHC 93 methods have gone largely unused and, in my laboratories, the extended HPHC methods have only been run a few times since method validation.

Table 2: Compounds on the FDA Abbreviated HPHC Cigarette Smoke List

Class	Compounds	Routine Methods-Pre-FDA
TNCO	Nicotine, Carbon Monoxide	Yes, Health Canada
Ammonia	Ammonia	Yes, Health Canada
Carbonyls	Acetaldehyde, Acrolein, Crotonaldehyde, Formaldehyde	Yes, Health Canada
Volatiles	1,3-Butadiene, Acrylonitrile, Benzene, Isoprene, Toluene	Yes, Health Canada
Nitrosamines (TSNAs)	4-(Methylnitrosamino)1-(3-pyridyl)-1butanone (NNK), N-Nitrosonornicotine (NNN)	Yes, Health Canada
PAHs	Benzo[a]pyrene	Yes, Health Canada
Aromatic Amines	1-Aminonaphthalene, 2-Aminonaphthalene, 4-Aminobiphenyl,	Yes, Health Canada

Tobacco Control Act (2013-2016)

In 2012, analysis of samples for abbreviated HPHC reporting consumed the majority of the industry capacity. Our facilities hired additional staff and added extra shifts to meet the demand for testing. However, this testing requirement ended in December of 2012 and due to delays in reviewing SE applications, we saw about a 25% drop in revenue in 2013 as compared to 2012. Across the industry, capacity was reduced in 2013 due to reduced testing demand.

In early 2014 the industry started to see an increase in FDA review of SE applications. The 2012 abbreviated HPHC list became the standard list for testing both current and predicate products. Projects were largely driven by gathering the data needed for new SE applications or responding to FDA's questions raised during the review of pending SE applications. We also started to see a large number of projects related to product stewardship testing for e-vapor products including e-liquids and also pre-filled devices. The body of literature on e-vapor products greatly expanded during this time and the industry began to shift from standard assays like nicotine and diacetyl testing to more complex assays including metals, nicotine degradants, and also long-term stability studies on finished goods. While e-vapor projects still tended to be limited in scope compared to combustible products, the number of clients and the range of products (flavors and nicotine content) meant that e-vapor testing began to surpass combustible testing for the first time.

Tobacco Control Act (May 2016-Present)

On May 10, 2016, the FDA issued a final rule deeming that all electronic nicotine delivery systems (ENDS), cigars, hookah, pipe tobacco, nicotine gels, and dissolvables would be considered tobacco products and subject to the TCA

with an effective date of August 8, 2016. The broad scope of this new rule had a major effect on the e-vapor industry and CROs that served the industry. Unlike cigarettes, smokeless tobacco and cigars, e-cigarettes were not widely marketed in 2007 and thus were not suitable for the SE pathway. Instead, PMTA applications would need to be submitted to support these products with a due date of August 2018. The complexity of a PMTA application combined with both the expected cost and short time window to complete the application meant that the vast majority of the industry did not view submitting applications as a viable option. By some estimates, >99% of current ENDS manufacturers would not attempt to complete the PMTA process. In our laboratories, a decline in e-vapor testing supported the premise that the majority of companies would not or could not file a PMTA application. In one of our laboratories, the total number of e-vapor clients decreased by 92% from 2015 to 2017. This decline was driven by the requirement to report health related data to the FDA, lack of guidance and complexity of the PMTA process, and also the projected cost to complete a PMTA application.

Cigars were the other major market sector deemed in the 2016 TCA rule. Unlike E-vapor products, cigars were well established on the US market in 2007 and both the grandfather and SE pathways were open to cigars. SE applications would need to be submitted to support these products with a due date of August 2018. The number of cigar brands and sub-brands on the US market could have potentially provided a major influx of testing to the CRO industry but several issues prevented that from being the reality. Given the short two-year window, testing capacity would have been exceeded if all the products on the market were tested for the abbreviated HPHC list. However, there was very little industry interest in testing cigars in 2016. Testing requirements for cigarettes were defined in the 2012 Guidance for Industry which included the list of compounds, smoking conditions, and also the number of required replicates. Guidance for cigarette SE applications were published in September of 2011 (2) with later updates in 2015 and 2016 (9). However, unlike cigars, cigarettes have a long history of routine testing from FTC testing to Health Canada HPHC reporting. Cigarettes are also less diverse than cigars. Cigars range from small machine-made, filter-tipped products to long filler, premium cigars. Since there are many differences between cigars and cigarettes, the existing HPHC and SE guidance documents for cigarettes cannot be directly applied to cigars. Open questions remain around which smoking regime and HPHCs to include in a cigar SE submission. This lack of clarity is delaying the submission of SE applications to the agency.

Another issue that has faced the CRO industry is the uncertainty around testing deadlines and extension of those deadlines. The deadline to file all PMTA and SE applications by August of 2018 was extremely aggressive given the huge number of e-liquids, e-vapor devices and cigars that are currently marketed in the US. The number of cigar brands and sub-brands easily dwarfs the number of cigarette

brands on the US market and while accurate numbers do not exist, it was reported in 2014 that 7,764 unique e-liquid flavors existed with 242 new flavors being added each month (10). Given the lack of FDA guidance and unrealistic timeline, it came as little surprise that extensions were granted by the FDA for both SE and PMTA applications. In May 2017, the FDA published the first guidance document which provided a three-month extension of all future compliance deadlines for requirements under the final deeming rule. The May 2017 guidance applied to all categories of newly regulated products, including ENDS (*e.g.*, e-cigarettes and e-cigars), hookah, pipe tobacco, and cigars. In August of 2017, the compliance dates were extended to August 8, 2021 (combustible tobacco products) and August 8, 2022 (noncombustible tobacco products) (11). The end result of these extensions was that companies were given an additional three or four years to complete their SE or PMTA applications. This time was clearly needed in order to allow the agency to publish guidance documents and also allow time for the industry to generate the information needed to submit SE or PMTA applications. Unfortunately, the extensions had a negative impact on CROs that had just prepared to meet the FDA's aggressive timelines. While it is clear that the goal of the extensions was to provide the industry more time to prepare SE and PMTA applications, without clear guidance from the agency, product testing will remain on hold until guidance is published.

HPHC testing of E-cigarettes

In May 2016, the FDA published a draft guidance document on Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems (12). This document outlined the information required to support regulatory filings on e-cigarettes including a list of recommended HPHC compounds. Unlike the 2011 HPHC list, a TPSAC was not convened to draft this list so there was no advance notice of potential compounds for inclusion on the HPHC list. The list of compounds is shown in Table 3.

Table 3: Compounds on the FDA e-cigarette HPHC List

Class	Compounds	Routine Methods Pre-PMTA
Primary Constituents	Nicotine, Propylene glycol, Glycerin, Menthol and Water	Yes
Liquid Contaminants	Ethylene glycol and Diethylene glycol	No
Nicotine Related	TSNAs and Anabasine	Yes
Aromatic Amines	1-Aminonaphthalene, 2-Aminonaphthalene and 4-Aminobiphenyl	No
Polynuclear Aromatic Hydrocarbons (PAHs)	Benzo[a]pyrene	No

Volatiles	1,3-Butadiene, Acrylonitrile, Benzene, Isoprene and Toluene	No
Ammonia	Ammonia	No
Carbonyls	Acetaldehyde, Acrolein, Crotonaldehyde, Formaldehyde and Diacetyl	Yes
Metals	Arsenic, Cadmium, Chromium, Lead, Nickel and Zinc	Yes

The list of compounds was released 29 months before the deadline to submit PMTA applications. Only four of the nine classes of compounds (primary constituents, TSNAs, anabasine, carbonyls, and metals) were routinely analyzed before the PMTA guidance. The other methods had to be developed and validated before routine testing could begin. The end result is that the original PMTA compliance window was reduced from an already short 29 months while the laboratories prepared for the required testing. Having a transparent and open process would have greatly aided the industry, as was done with the original HPHC list, and would have allowed more time to develop methods and prepare for testing of e-cigarettes and e-liquids. While the agency did provide a list of target compounds, there has been limited guidance on how to collect samples from e-cigarettes. Instead, the agency provided the following general statement on product testing.

> "Evaluating new tobacco products under a range of conditions, including both non-intense (*e.g.*, lower levels of exposure and lower volumes of aerosol generated) and intense (*e.g.*, higher levels of exposure and higher volumes of aerosol generated), enables FDA to understand the likely range of delivery of emissions."

While there is certainly some logic behind the requirement to test under both low and high levels of exposure, topography studies will likely be required to determine actual puffing conditions that lead to low or high levels of exposure. The request to test products under a range of conditions for each device instead of preset machine puffing conditions adds an extra layer of complexity and delay to the start of the testing required to file a PMTA application.

Reporting of HPHCs in Newly Deemed Products

In Section 904 of the TCA, there is a requirement that 3 years after deeming, HPHCs in each tobacco product must be supplied to the agency, for each brand and subbrand. This includes all e-cigarettes, e-cigars, hookah, pipe tobacco, and cigars on the market prior to August 2016. The agency granted a three-month extension and these reports are currently due in November 2019. However, to date there has been little guidance on how to generate the requested information to the agency. For example, the list of HPHCs required for each class of newly deemed

products has not been issued by the agency, and conditions for generating smoke or aerosol samples has also not been published by the agency. The uncertainty surrounding product testing requirements has led to few manufacturers being willing to proceed with testing until more guidance is issued by the agency. Due to these delays, once guidance is issued, it is almost certain that there will not be enough capacity to provide analytical testing on all products on the US market by November 2019.

Conclusion

The main challenge of any testing laboratory is to provide appropriate testing services in a timely manner. This applies to both internal and external providers of testing services. The difficult balancing act for CROs is to have enough resources to supply what is needed to the clients while minimizing excess capacity. This includes managing both analytical methodologies and also testing capacity. Since 2009, the tobacco CRO industry has been faced with a very difficult situation of trying to predict and prepare for possible FDA requirements while also maintaining company performance. The agency is very aware that the small or independent manufactures do not have internal capabilities and rely on CROs for virtually all regulatory testing. To help alleviate capacity limitations, the agency has granted extensions and reduced the testing burden. However, the factor that is limiting capacity in the industry, both internal and external, is uncertainty around testing requirements and also timing of testing. Clarity of testing requirements and also longer compliance windows will lead to more capacity in the industry. Guidance from the agency will lead to more time to both prepare and complete the required product testing. Currently, guidance is needed for all newly deemed products including cigar SE and e-vapor PMTA applications. Lack of guidance is leading to a reduction in overall testing capacity since CROs are hesitant to add capacity without some certainty around future testing requirements. Based on past agency performance, it is expected that future compliance windows will be artificially compressed which will further reduce overcall capacity. Timely and appropriate guidance from the agency will benefit not only the CRO industry but also the manufacturers and ultimately the agency.

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