Altria
Altria Client Services

Product Integrity
Review and Toxicological Evaluation Guideline

Smokeless Tobacco Products: Test Articles, Prototypes, and Products

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1 Introduction

A toxicological evaluation serves as the mechanism for providing guidance regarding the suitability for use of product components, packaging or manufacturing materials, processes, integrated technologies and integrated product designs. The Product Integrity Toxicological Evaluation Guidelines describe the basic approaches used in this evaluation. The guideline structure includes an over-arching decision making flow framework[1] and the associated platform-specific guideline documents.

This guideline describes the minimum requirements and basic review approaches necessary to complete a PI evaluation of product development activities which result in smokeless tobacco test articles, prototypes or products.

2 Purpose

The purpose of this guideline is to describe an evaluation approach to reviewing test articles, products and prototype designs to be used by personnel involved in research and development activities, participants involved in consumer acceptability testing, and consumers following the market release of a product.

The goal of the evaluation process is to provide a consistent, logical, and documented evaluation approach. As part of the process, a toxicological evaluation is conducted to provide reasonable certainty that the product or product design will not increase the risk beyond that recognized for currently available marketed products (*e.g.*, similar smokeless tobacco products). A weight of evidence evaluation process is used where sound scientific judgment is critical along with recognition of uncertainties in the evaluation.

The review process is also intended to assure compliance with applicable laws and regulations. Additional specific Principles, Policies and Quality Management System (QMS) procedures are referred to but not restated in this document. Critical Control Point Management (CCPM) systems and specific laboratory methods, which are referred to in this guideline, reside within other parts of the company. (See Appendix A for definitions.)

This document is a guideline and as such is intended to meet the majority of research and product development needs. It is intended to set general requirements. Since not all situations can be predicted, it may be necessary from time to time to develop and document unique evaluation approaches that may be outside the structure of this guideline document. With this in mind, it may occasionally be necessary to conduct assessments in a manner different from those detailed here.

[1] Product Integrity-Toxicological Evaluation Framework Overview

Product Integrity will make every effort to assure that the requirements of the evaluation approach are completed and will provide a scientifically-based assessment if, or when, it becomes necessary to modify the routine approach described by this guideline.

3 Scope

The guideline is intended to address evaluations which occur at various stages of the Product Development and Technology Development Processes. During this process research and consumer testing of smokeless tobacco product test articles, prototypes or products occurs. The evaluations are not intended to be quality assurance checks on a lot-by-lot or batch-by-batch basis, but rather are intended to review the intended designs and product components of prototypes, technologies and processes used to develop final products.

Evaluations addressed by this guideline specifically include assessment of levels of various chemical constituents and parameters in smokeless tobacco test articles, prototypes and products that have been identified as health-relevant by various public health authoritative bodies including the International Agency for Research on Cancer (IARC), the U.S. Surgeon General, the World Health Organization (WHO), and the U.S. National Cancer Institute (NCI). In some instances *in vitro* assessments are included in the evaluation. Smokeless tobacco test articles, prototypes, products and processes are additionally monitored for the presence of various microbial species using approaches similar to those used in the food industry.

Specific items for evaluation include but are not limited to:

Tobacco (*e.g.*, blends, types, processing)

Directly added individual non-tobacco ingredients

Formulations

Test articles, prototypes and products

Processes used in sample and product preparation

Items used for indirect contact (processing materials)

Packaging (product contact items)

4 Evaluation Approach Fundamentals

4.1 Basic Elements

While PI maintains responsibility for the evaluation process and final review for adherence to this guideline, there are many partners in such an effort. Applicable SOPs,

guidelines, work instructions and other documentation describing associated activities within this guideline reside within those individual departments.

The basic elements of the evaluation are:

1. **Control:** Processes and procedures to assure that knowledgeable personnel are making correct decisions, proposed testing is adequately designed and monitored, and that risk has been assessed and appropriately mitigated. Procedures to assure proper preparation and control of test articles during the development cycle. Responsibility in this area is shared among the RD&E product development teams with input from PI and others.

2. **Ingredient and process review:** Processes and procedures to assure an appropriate level of safety for all parts of a test article, prototype or product. This is a role assumed by PI.

3. **Information:** Processes and procedures to assure that information, as defined in the Altria Group, Inc. Product Communication Principle and associated policies, is provided to the study coordinators such that consumers or participants in a study can be provided correct and adequate information regarding potential risk.

4. **Facility:** Processes and procedures to assure that the facilities used to prepare test articles, prototypes or products meet certain sanitation and quality requirements. These considerations are also made by the Quality Department, Product Regulatory Compliance, and RD&E Quality groups along with the RD&E product development teams.

As indicated previously, a variety of documents and processes describing elements of the evaluation are institutionalized within other parts of the Company. Therefore, they will not be described in detail here, but rather will be used to illustrate the progression of rigor required as product development activities progress from controlled testing by individuals who possess knowledge about the product to uncontrolled, extended use testing by less knowledgeable groups.

4.2 Testing Approaches

As described in the Product Integrity Toxicological Evaluation Decision Making Framework Overview and associated flow chart, the amount of data collected and testing needed to make a decision will depend on such things as the potential exposure, the history of use, current use status (new vs. currently used)and the use level. Most toxicologic evaluations will utilize data obtained from multiple sources.

Product development generally follows a progression of research and development activities starting with the researchers who work in laboratory conditions preparing small scale samples for limited individual testing. This activity then proceeds through situations where small groups of trained internal and external panelists participate in the product development sensory evaluations, and eventually on to consumer testing. This approach will be applied to testing of smokeless tobacco test articles, prototypes and products. The general categories for these approaches are outlined in the Product Integrity Guidance Document: Subjective Evaluation Panel Designations, and can be generally described as:

1. **Development or Research Personnel:** These individuals generally work within the research and development areas, are involved in preparing and tasting test samples and prototype creations and are specifically assigned to a developmental project.

2. **Recurrent or Trained Panel:** These panels may comprise employees of the Altria Group and its Companies, externally recruited consumer participants, or certain external third party individuals contracted to conduct specific product development activities.

3. **Controlled Consumer Acceptability Panel:** These groups are involved in sensory evaluations or studies involving development of some specific product attribute such as liking or sensory acceptability. They consist of individuals recruited from outside of the Altria Group and its Companies who have no previous knowledge of the test article, prototype or product.

4. **Uncontrolled Consumer Acceptability Panel:** These groups are involved in product acceptability, sensory or marketing evaluations and the studies they participate in are commonly referred to as Public Opinion Labs (POLs), or Home Use Testing (HUT). They consist of selected consumers who have no previous knowledge of the test article, prototype or product.

5. **Test Market/Commercialization:** Exposures for these individuals are self-controlled or guided by product messaging. Consumers will purchase products that have been prepared in a facility that meets sanitation and contamination control practices for a tobacco.

5 PI Review and Toxicological Evaluation

Evaluation decisions will generally rely on a standard of *no more risk than commonly encountered from other available smokeless tobacco products used under similar circumstances*. The level of risk tolerance is assessed by a combination of available hazard information, level of understanding by the participants in the group to be exposed, amount of potential exposure, route of administration, and control of the exposure

situation. The evaluation should consider acceptable daily intake values (if available) and prior history of use for comparable products or testing situations. By demonstrating the substantial equivalence to these commonly available smokeless tobacco products, it may be assumed that a new product would present no more risk than commonly encountered by consumers of these commercially marketed products.

5.1 Weight of Evidence / Scientific Judgment

Since most evaluations will utilize data obtained from multiple sources of both a chemical and biological nature, the toxicological evaluation will consider relevant available data including the scientific strength of the results and the appropriateness of the testing methodologies to make a determination of substantial equivalence to currently available marketed products. Testing is not necessarily always conducted on final product designs. In many cases, well designed technology assessments using processes, ingredients, and/or tobacco blends representative of those used in the final product, may be employed to generate sufficient data for evaluation. For these situations, a limited analysis incorporating elements of the technology evaluation may be warranted to assure that the final product complies with the finding of a previous assessment.

For non-tobacco ingredients which have been approved for use in foods as either Food and Drug Administration (FDA) food additives or are affirmed "Generally Recognized as Safe" (GRAS) by a consensus among qualified experts (*e.g.*, Flavor and Extract Manufacturers Association (FEMA) panel), the appropriateness for use in a smokeless tobacco product will be evaluated based upon identified limitations such as acceptable daily intake levels, ingredient functionality descriptions, and product category designations. In addition to the toxicological assessment, PI may also evaluate use of an ingredient based upon business concerns.

Presently there are no established criteria or methodologies that encompass the expected variability of exposure to smokeless tobacco products, nor are there biological models that specifically predict the range of health effects associated with smokeless tobacco product use. Given this lack of established assessment tools, chemical analysis and surrogate biological testing models are employed in this evaluation process. However, there is some inherent uncertainty associated with interpretations of such test results as indications of the outcomes potentially associated with human exposure.

Generally, no single factor (*i.e.*, endpoint or assay result) can determine the overall weight of evidence conclusion, and therefore the available data are judged holistically. Weight of evidence relies upon the expert judgment of a properly trained and experienced reviewer to evaluate the existing data and formulate rational conclusions. A critical element of the evaluation procedure is the application of sound scientific judgment based on knowledge of the variability and predictive power of the biological assays, as well as the variability of tobacco and its inherent toxicological characteristics. Only those individuals with adequate training and experience (*i.e.*, credentialed according to the current credentialing guidelines for PI) will be allowed to make decisions regarding the

evaluation. The evaluation procedure is an iterative process. Initial views, conclusions and approaches may change from time to time as new information is incorporated into the evaluation procedure.

5.2 Commercial Reference Products

The assessment process for smokeless tobacco products is grounded in the concept of equivalence to typical smokeless tobacco products currently available to consumers in the United States. It is therefore important that some benchmark of competitors' products be periodically conducted to understand the range and variability of the individual samples which define the market. It is also important to gather data from a representative sample of products that represent a cross-section based on pre-defined characteristics. The choice of appropriate commercial reference products should consider:

- Design elements
- Tobacco composition and processing
- Flavor attributes
- Intended use properties

The types of data collected and the level of testing varies for the different exposure situations. The determination of which endpoints will be required for product assessment will be made on a case-by-case basis. This determination will be made using scientific judgment taking into account current knowledge about product prototypes and the nature and magnitude of modifications to such prototypes during the product development process. A standard list of chemical and biological endpoints is shown below. These, or a selected subset of these, analytes will serve as the primary basis of market comparison.

Table 1: Analytes that may be included in comparative analysis of product, test article or prototype:

Endpoint		
Nicotine	NAT*	Nickel
Tobacco pH	Total TSNA*	Chromium
Moisture	Nitrite	Microbiology**
NDMA*	B(a)P	Water activity
NNN*	Cadmium	Biological (*e.g.*, EpiOral assay)***
NNK*	Lead	
NAB*	Arsenic	

***NDMA:** N-Nitrosodimethylamine, **NNN:** N-Nitrosonornicotine, **NNK:** 4-(N-Methyl-N-nitrosamine)- 1 -(3-pyridyl)- 1 -butanone, **NAB**: N-Nitrosoanabasine, **NAT**: N-Nitrosoanatabine, **TSNA**: Tobacco Specific Nitrosamine

**See PI Guidance for Microbiological Testing on Smokeless Tobacco Products

***Klausner, M., Ayehunie,S., Breyfogle, B.A., Wertz, P.W., Bacca, L., Kubilus, J., 2007. Organotypic human oral tissue models for toxicological studies. Toxicology in Vitro 21, 938-949.

Assessment of these analytes may also be useful in providing data necessary for weight of evidence purposes.

6 Standards for Intended Use Evaluations

The purpose of this evaluation is to mitigate risk. PI follows a risk assessment evaluation approach requiring more rigor as the number of human exposures increases, number of samples increases, and/or amount of control of the use of the product decreases.

With the exception of some Designated Developer, Researcher and Recurrent or Trained Panel activities, described below, notification of a planned consumer study will be submitted to PI for evaluation prior to conducting the study. Information generally requested as part of the submission includes a list of intended ingredients, processing steps, known hazards, warnings, instructions, study design, number of samples to be used, and number of participants. The evaluation will start by considering suitability of individual ingredients and processes for the intended use in the anticipated design and will progress in a step-wise manner leading to the final formulation and/or product evaluation.

The following sections describe the requirements for the various basic elements of the evaluation prior to approval of testing involving human exposure. (Note: Some activities necessary to complete the evaluation are not directly under PI control, but will be addressed as part of the responsibilities of the researcher or project team assigned to the product development activity.)

6.1 Development or Research Personnel

6.1.1 *Control*

Sample Monitoring: Prototype construction should be documented and traceable.

Hazard Identification: Personnel should be aware of product hazards including identification of any relevant microbiological issues, ingredient limitations or general product safety issues and should contact PI if a question regarding the safe use of any ingredient or process arises.

Because of the very early development stage, special hazard identification procedures are not required at this point unless a critical element is identified during the preliminary hazard identification process.

6.1.2 *Ingredient & Process Review*

NOTE: If at any time Development or Research Personnel have a question regarding the safe use of any ingredient, formulation or process they should contact PI. In addition, once a material has been evaluated and approved by PI it may be used in smokeless tobacco test articles, prototypes and products consumed by Development or Research Personnel or Recurrent or Trained Panels with adherence to any limitations identified in the approval notes.

Non-tobacco Ingredients: The following will be considered acceptable for use in smokeless tobacco test articles, prototypes or products by Development or Research Personnel at levels appropriate to the food use status and exposure condition:

- Ingredients which have received prior approval by the FDA for use in foods
- Ingredients which are affirmed GRAS for use in foods by a consensus among qualified experts

PI does reserve the option to review all non-tobacco ingredients and other materials in use by the Development or Research Personnel to assure safe use. When these are deemed unsafe or questionable by PI, even when affirmed GRAS (*e.g.*, very limited scientific data available or questionable GRAS process documentation), they will be removed from general use until such time that a sufficient determination regarding their use can be made.

Non-tobacco ingredients that do not qualify as approved food additives or are not affirmed GRAS for use in foods will be reviewed by PI for suitability for use by Development or Research Personnel.

Processing: Processing information should be submitted for PI review for any new processes or if a question regarding safe use of the process is identified during hazard identification. Test articles developed using PI-approved processes and ingredients do not require PI review at this test level.

Vendors: Vendors meeting the following criteria will be considered acceptable sources for ingredients for Development or Research Personnel use.

1. Reputable ingredient manufacturer or commercial food outlet. (Note: The assumption is that these items are lawful foods; meaning that they are not adulterated or misbranded, provide allergenicity statements, and are comprised of approved food ingredients and/or ingredients affirmed GRAS.)
   …or…
2. Vendors for whom the quality review process has been initiated and there is a history of use.
   …or…
3. Vendors who are considered to be qualified by virtue of completing the ALCS audit review process.

Non-tobacco ingredients obtained from vendors who do not meet these vendor criteria will be reviewed to assess acceptability prior to use by the Development or Research Personnel.

Product Characterization: Ingredients which meet the above criteria will be acceptable for Development or Research Personnel use without additional PI review for formulations when used at levels limited to the minimum quantity required to evaluate product attributes under development. Labels or vendor documents should be available to provide notification of unique hazards, special handling criteria or allergenicity issues.

Market Comparison Testing: There is generally no market comparison testing conducted for the Development or Research Personnel level subjective evaluation.

6.1.3 *Information*

Voluntary Participation: Development or Research Personnel will have a documented understanding of their job requirements and limitations as specified in their job descriptions. Their use of smokeless tobacco products is voluntary and they are encouraged to seek PI review when they need additional information.

Labeling and Warnings: Specific labeling requirements for laboratory samples will follow standard laboratory safety practices. Samples containing ingredients that have allergens (*i.e.*, allergens and their associated proteins as defined by the FDA) present, will require a specific label to this effect. In addition notification will be made if the product is known to contain any non food-approved materials.

Adverse Events: Any adverse events experienced by the Development or Research Personnel during their research activities must be immediately reported to the project leader and managed in accordance with applicable procedures set forth in the appropriate Emergency Management PPI and the PI Pre-Market Reported Physical Effect (RPE) Collection, Compilation and Evaluation Process.

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6.1.4 *Facility*

Sanitation: Samples consumed by Development or Research Personnel will be prepared in a facility which meets sanitation and contamination control requirements for tobacco and monitored on a regular schedule. The Development or Research Personnel will maintain expertise in and follow the sanitation requirements as part of the QMS.

Personnel should be aware that preparation techniques, improper storage or unsanitary conditions may lead to the presence of microbiological hazards. The need for more rigorous sanitation or handling requirements specific to an individual ingredient,

prototype or product will be assessed by the Development or Research Personnel in consultation with the Quality Department and PI as necessary.

Microbial and Pesticide Monitoring: Microbial and pesticide monitoring activities will be dependent upon the quality and hazard associated with the ingredient or source. For most anticipated situations, depending on the relative intrinsic hazards of a particular ingredient, when ingredients are obtained from reputable food suppliers or qualified vendors, ingredient specific microbial and pesticide monitoring is unnecessary. Monitoring activities will instead rely on routine facility monitoring practices. However, individual monitoring may be necessary when unique vendor sources are used, there is a question regarding proper storage or processing, and/or unique hazards are identified.

6.2 Recurrent or Trained Panel

6.2.1 *Control*

Sample Monitoring: Prototype construction should be documented and traceable.

Hazard Identification: A preliminary hazard analysis (PHA) process should be conducted including identification of any relevant microbiological issues, ingredient limitations or general product safety issues to identify any initial hazards that might be present which might require specific material handling or treatment process, or warnings. Efforts to control these risks by investigating alternative approaches for sample production should be addressed prior to conducting Recurrent or Trained Panel testing.

Because of the very early development stage, special hazard identification procedures are not required at this point unless a critical element is identified during the preliminary hazard identification process.

6.2.2 *Ingredient & Process Review*

The trained researcher preparing samples for Recurrent or Trained Panels should have demonstrated and documented training, education and experience in relevant areas of tobacco product quality standards, handling, and preparations. The researcher must also be aware of and comply with the guidance outlined in the Altria Group, Inc. Consumer, Trend Scanning and Clinical Research Principle and the associated policies. Formulations prepared using previously evaluated and approved ingredients may be given to Recurrent or Trained Panels without additional review by PI.

Non-tobacco Ingredients: The following will be considered acceptable ingredients for use in smokeless tobacco test articles, prototypes and products for use by the Recurrent or Trained Panels at levels appropriate to the food use status and exposure condition:

- Ingredients that have received prior approval by the FDA for use in foods

- Ingredients which are affirmed GRAS for use in foods by a consensus among qualified experts

Non-tobacco ingredients must be evaluated by PI and deemed acceptable prior to use by a Recurrent or Trained Panel.

Non-tobacco ingredients that do not qualify as approved food additives or are not affirmed GRAS for use in foods will be reviewed by PI for suitability for Recurrent or Trained Panel use.

Processing: Processing information should be submitted for PI review for any new processes or if a question regarding safe use of the process is identified during hazard identification.

Vendors: Vendors meeting the following criteria will be considered acceptable sources for Recurrent or Trained Panel use.

1. Reputable ingredient manufacturer or commercial food outlet (Note: The assumption is that these items are lawful foods; meaning that they are not adulterated or misbranded, provide allergenicity statements, and are comprised of approved food ingredients and/or ingredients affirmed GRAS.)
   …or…
2. Vendors for whom the quality review process has been initiated and there is a history of use.
   …or…
3. Vendors who are considered to be qualified by virtue of completing the ALCS audit review process.

Non-tobacco ingredients obtained from vendors who do not meet these vendor criteria will be reviewed to assess acceptability prior to use by the panel members.

Product Characterization: PI approved ingredients which meet the above criteria will be acceptable for Recurrent or Trained Panel use without additional PI review for formulations when used at levels limited to the minimum quantity required to evaluate product attributes under development and within any use limitations identified in the approval notes. Labels or vendor documents should be available to the participants to provide notification of any unique hazards, special handling criteria or allergenicity issues.

Market Comparison Testing: There is generally no market comparison testing conducted for the Recurrent or Trained Panel level subjective evaluation unless the effect of changes to the test article cannot be predicted based on previous data.

6.2.3 *Information*

Voluntary Participation: Participants will be informed and such activity documented as described in the ALCS Consumer, Trend Scanning and Clinical Research Processes and Standards Policy.

Labeling and Warnings: As defined in the Altria Group, Inc. Product Communications Principle and associated policies, consumers or participants in a study will be provided information regarding potential risk.

Adverse Events: Any adverse events reported by a participant must be immediately reported to the project leader and managed in accordance with applicable procedures set forth in the PI Pre-Market Reported Physical Effect (RPE) Collection, Compilation and Evaluation Process and, for employees, in the appropriate EH&S Emergency Management Policy.

6.2.4 *Facility*

Sanitation: Prototypes intended for Recurrent or Trained Panel will be prepared in a facility which meets sanitation and contamination control practices for tobacco. The developer will maintain expertise in and follow the sanitation requirements as part of the QMS.

Personnel should be aware that preparation techniques, improper storage or unsanitary conditions may lead to the presence of microbiological hazards. The need for more rigorous sanitation or handling requirements specific to an individual ingredient, prototype or product will be assessed by the developer in consultation with the Quality Department and PI as necessary.

Microbial and Pesticide Monitoring: Microbial and pesticide monitoring activities will be dependent upon the quality and hazard associated with the ingredient or source. For most anticipated situations, depending on the relative intrinsic hazards of a particular ingredient, when ingredients are obtained from reputable food suppliers or qualified vendors, ingredient specific microbial and pesticide monitoring is unnecessary. Monitoring activities will instead rely on routine facility monitoring practices. However, individual monitoring may be necessary when unique vendor sources are used, there is a question regarding proper storage or processing, and/or unique hazards are identified.

6.3 Controlled Consumer Acceptability Panel

6.3.1 *Control*

Protocol: Protocols and procedures are developed for these panels consistent with the elements in the ALCS Consumer, Trend Scanning and Clinical Research Processes and Standards Policy.

Sample Monitoring: Prototype construction should be documented and traceable.

Hazard Identification: A product specific hazard analysis plan should be prepared identifying any relevant microbiological issues, ingredient limitations or general product safety issues, and all necessary specific material handling or treatment process, or warnings. Special hazard identification procedures should be completed by the project team as part of the hazard identification process to address potential risks which may occur as part of the Controlled Consumer Acceptability Panel testing.

6.3.2 *Ingredient & Process Review*

For Controlled Consumer Acceptability Panels, all ingredients, formulations, and processes involving ingredients used to make the product as well as packaging will require PI review and approval prior to release to the panel.

Non-tobacco Ingredients: The following will be considered acceptable ingredients for use in smokeless tobacco test articles, prototypes and products for use by Controlled Consumer Acceptability Panels at levels appropriate to the food use status and exposure condition:

- Ingredients that have received prior approval by the FDA for use in foods
- Ingredients which are affirmed GRAS for use in foods by a consensus among qualified experts

Non-tobacco ingredients will be reviewed by PI and deemed acceptable prior to Controlled Consumer Acceptability Panel use. Individual ingredients of a formulation should be reviewed prior to the review of the formulation.

Processing: Processing information should be submitted for PI review for any new processes or if a question regarding safe use of the process is identified during hazard identification.

Vendors: Vendors meeting the following criteria will be considered acceptable sources for Controlled Consumer Acceptability Panel use:

1. Reputable food ingredient manufacturer. (Note: The assumption is that these items are lawful foods; meaning that they are not adulterated and not misbranded, provide allergenicity statements, and are comprised of approved food ingredients and/or ingredients that are affirmed GRAS.)

…or…

2. Vendors who have completed a vendor review and have supplied basic ingredient information.

…or…

3. Vendors who are considered to be qualified by virtue of completing the ALCS audit review process.

Product Characterization: Identification of ingredients and other materials used in the product such as formulations with anticipated use levels, and manufacturing processes will be submitted to PI for review.

Information from the vendor concerning the non-tobacco material will generally include:

- Ingredient specification
- Microbial certificate of analysis (if applicable)
- Continuing Guarantee
- FDA/FEMA GRAS statement
- Allergen statement
- MSDS (if applicable)
- FDA Ingredient Declaration statement

Market Comparison Evaluation: Market comparison evaluation for equivalency will be conducted on prototypes, products, tobacco fillers or blends using commercial reference products available to consumers in the United States prior to Controlled Consumer Acceptability Panel testing. Elements that may be included in the market comparison testing are shown in section 5.2- Table 1. Data used may be developed from final product testing or blend analysis.

6.3.3 *Information*

Voluntary Participation: Participants will be informed and such activity documented as described in the ALCS Consumer, Trend Scanning and Clinical Research Processes and Standards Policy.

Labeling and Warnings: As defined in the Altria Group, Inc. Product Communications Principle and associated policies, consumers or participants in a study will be provided information regarding potential risk.

Adverse Events: Any adverse events reported by a participant must be immediately reported to the study leader and managed in accordance with applicable procedures set forth in the PI Pre-Market Reported Physical Effect (RPE) Collection, Compilation and Evaluation Process.

6.3.4 *Facility*

Sanitation: Prototypes intended for Controlled Consumer Acceptability Panels will be produced in a facility that meets sanitation and contamination control practices for a tobacco facility.

Microbial and Pesticide Monitoring: Preparation techniques, improper storage or unsanitary conditions may lead to the presence of microbiological hazards. Samples intended for Controlled Consumer Acceptability Panels will be subjected to a "lot by lot" microbiological screen unless it is demonstrated that the microbiological hazards do not exist by virtue of adequate treatment techniques (*e.g.,* repeated batch analysis of the intended production process), or physical improbability (ingredient and/or chemical content) such that microbiological growth is not expected.

Pesticide monitoring activities will rely on any routine vendor facility monitoring practices. However, individual pesticide monitoring may be necessary when unique vendor sources are used.

6.4 Uncontrolled Consumer Acceptability Panels

6.4.1 *Control*

Protocol: Protocols and procedures are developed for these panels consistent with the elements in the ALCS Consumer, Trend Scanning and Clinical Research Processes and Standards Policy.

Sample Monitoring: Prototype construction should be documented and traceable.

Hazard Identification: A product specific risk analysis plan (*e.g.,* CCPM, PHA) will be initiated to identify any specific hazards that require remediation prior to production. Microbiological hazards related to processing should be considered and mitigated through efforts to control risk by investigating alternative processing approaches.

Special hazard identification procedures will be completed as part of the hazard identification process to identify and address risk which may occur as part of the Uncontrolled Consumer Acceptability Panel testing.

6.4.2 *Ingredient & Process Review*

For Uncontrolled Consumer Acceptability Panels, all ingredients, formulations, and processes involving ingredients used to make the product as well as packaging will require PI review and approval prior to release to the panel.

Non-tobacco Ingredients: The following will be considered acceptable ingredients for use in smokeless tobacco test articles, prototypes and products for use by Uncontrolled

Consumer Acceptability Panels at levels appropriate to the food use status and exposure condition:

- Ingredients that PI has determined to have received prior approval by the FDA for use in foods
- Ingredients which are affirmed GRAS by a consensus among qualified experts

Wherever possible, non-tobacco ingredients which are not approved for use in foods will not be used. PI will prepare appropriate documentation to address situations where use of a non-GRAS material is deemed necessary.

For packaging materials used for uncontrolled consumer acceptability panel samples of smokeless tobacco products, PI relies on the existing regulations for food-use packaging. Materials approved for use in food packaging will be used in the packaging of these products.

Processing: Processing information should be submitted for PI review for any new processes or if a question regarding safe use of the process is identified during hazard identification.

Vendors: Vendors who are considered to be qualified by virtue of completing the ALCS audit review process and supplied specific ingredient information will be considered acceptable sources of ingredients for Uncontrolled Consumer Acceptability Panel use.

Product Characterization: Identification of ingredients and other materials used in the product and packaging such as: formulations with anticipated use levels, packaging materials and inks, and manufacturing processes will be submitted to PI for review.

Information from the vendor concerning the material will generally include:

- Ingredient specification
- Microbial certificate of analysis (if applicable)
- Continuing Guarantee
- FDA/FEMA GRAS statement
- Allergen statement
- MSDS (if applicable)
- FDA Ingredient Declaration statement. or Quantitative disclosure

Market Comparison Testing: Market comparison evaluation for equivalency will be conducted on prototypes, products, tobacco fillers or blends using commercial reference products available to consumers in the United States prior to Uncontrolled Consumer Acceptability Panel testing. Elements that may be included in the market comparison testing are shown in section 5.2- Table 1. Data used may be developed from final product testing or blend analysis.

6.4.3 *Information*

Voluntary Participation: Participants will be informed and such activity documented as described in the ALCS Consumer, Trend Scanning and Clinical Research Processes and Standards Policy.

Labeling and Warnings: As defined in the Altria Group, Inc. Product Communications Principle and associated policies, consumers or participants in a study will be provided information regarding potential risk.

Adverse Events: Adverse events reported by participants will be monitored through the study contractor and managed in accordance with applicable procedures set forth in the PI Pre-Market Reported Physical Effect (RPE) Collection, Compilation and Evaluation Process.

6.4.4 *Facility*

Sanitation: Prototypes intended for Uncontrolled Consumer Acceptability Panels will be produced in a facility that meets sanitation and contamination control requirements for a tobacco facility.

Microbial and Pesticide Monitoring: Potential microbiological hazards related to processing will be assessed as part of CCPM planning and mitigated through efforts to control risk by investigating alternative processing approaches or appropriate monitoring activities.

Pesticide monitoring activities will rely on the vendor's routine facility monitoring practices. However, individual pesticide monitoring may be necessary when unique vendor sources are used.

6.5 Test Market/ Commercialization

6.5.1 *Control*

Sample Monitoring: No specific monitoring requirements beyond standard QMS requirements for product are required.

Hazard Identification: Special hazard identification procedures will be completed as part of the hazard identification process to identify and address risk which may occur. A manufacturing facility product-specific risk plan (*e.g.*, CCPM, PHA) will be completed to identify and control any specific hazards that require remediation or monitoring.

6.5.2 *Ingredient & Process Review*

For Test Market and Commercialization, all ingredients, formulations, packaging, and processes involving ingredients used to make the product require PI review and approval.

Non-tobacco Ingredients: The following will be considered acceptable ingredients for use in smokeless tobacco products at levels appropriate to the food use status and exposure condition:

- Ingredients that PI has determined to have received prior approval by the FDA for use in foods
- Ingredients which are affirmed GRAS by a recognized scientific body for use in foods

Wherever possible, non-tobacco ingredients which are not approved for use in foods will not be used. PI will prepare appropriate documentation to address situations where the use of non-GRAS materials is deemed necessary.

For packaging materials used for commercialization/test market of smokeless tobacco products, PI relies on the existing regulations for food use packaging. Materials approved for use in food packaging will be used in the packaging of these products.

Vendors: Vendors who are considered qualified by virtue of completing the ALCS audit review process will be considered acceptable sources of ingredients for test market and commercialization.

Product Characterization: Identification of ingredients and other materials used in the product and packaging such as quantitative formulations with anticipated use levels, packaging materials and inks, and manufacturing processes will be submitted to PI for review.

Information from the vendor concerning the material will generally include:

- Quantitative disclosure
- Ingredient specification
- Microbial certificate of analysis (if applicable)
- Continuing Guarantee
- FDA/FEMA GRAS statement
- Allergen statement
- MSDS (if applicable)
- FDA Ingredient Declaration statement.

Market Comparison Testing: Market comparison evaluation for equivalency will be conducted on prototypes, products, tobacco fillers or blends using appropriate commercial reference product(s) prior to test market or commercial introduction unless

there is sufficient evidence from previous product/prototype testing to render such testing unnecessary.

6.5.3 *Information*

Voluntary Participation: Not applicable.

Labeling and Warnings: As defined in the Altria Group, Inc. Product Communications Principle and associated policies, consumers will be provided appropriate and adequate information regarding the product. These communications will satisfy applicable legal and Policy requirements and Company commitments.

Adverse Events: Adverse events will be reported and monitored through the Consumer Response Center.

6.5.4 *Facility*

Sanitation: All products will be prepared in a facility that meets sanitation and contamination control requirements for tobacco.

Microbial and Pesticide Monitoring: Potential microbiological hazards related to processing will be assessed as part of CCPM planning and mitigated through efforts to control risk by investigating alternative processing approaches or appropriate monitoring activities.

Pesticide monitoring activities will rely on the vendor's routine facility monitoring practices. However, individual pesticide monitoring may be necessary when unique vendor sources are used.

7 Guideline Evolution

The evaluation procedure will continue to evolve by developing and incorporating newer methodologies and approaches that are relevant to the evaluation process. With this perspective, it is expected that the methods and approaches used will vary from time to time as the Company continues to improve its evaluation procedure. Such evaluations may be triggered by regulatory developments, recommendations, industry guidance, or scientific practices.

8 Revision History

Revision #	Date	Reason for Revision
Prelim Guidance	1-30-07	PI Preliminary Guidance: A process for assessment of smokeless tobacco products
01		Original QMS document

9 Appendix A- Definitions

Allergen Statement (Sometimes "Oral Allergen Statement"): A document listing possible allergens, including milk, eggs, peanuts, tree nuts (such as almonds, cashews, and walnuts), fish (such as bass, cod, and flounder), crustacean (such as crab, lobster and shrimp), soybeans and wheat **and/or** any ingredient that contains protein derived from these food groups.

CCPM – Critical Control Point Management: CCPM is a systematic approach to the identification, evaluation and control of product safety hazards. CCPM is a system in which product safety is addressed through the analysis and control of biological, chemical and physical hazards of all production steps, including ingredients (raw material production), procurement, handling, distribution and consumption of the finished product. CCPM systems are validated through specific means and utilize seven principles to delineate product safety procedures. Note: CCPM is internal language for HACCP principles applied only to Smokeless Tobacco Products.

Continuing Guarantee: A document indicating that the ingredient specifically named is guaranteed not to be adulterated or misbranded within the meaning of the Federal Food, Drug and Cosmetic Act and that the ingredient may be introduced into interstate commerce.
This statement implies that:

- The ingredient meets food grade specifications
- The ingredient meets heavy metal requirements for foods
- The ingredient is microbiologically acceptable
- The ingredient meets pesticide residue requirements

Some reputable suppliers also indemnify and hold harmless the Purchaser against all damages or losses from the use of this ingredient if the ingredient is legally determined to be misbranded or mislabeled as provided to the Purchaser by the Supplier.

Disclosure: A quantitative list of chemicals and associated chemical abstract service (CAS) registry numbers describing a product component or material supplied by the manufacturer. May also contain trade names of products used by the manufacturer. The disclosure may be qualitative for early review and internal subjective evaluation.

GRAS - Generally Recognized As Safe: Designation that a chemical or substance added to food is generally recognized, among experts qualified by scientific training and experience to evaluate their safety, as having been shown through scientific procedures or through experiences based on common use in food (used in food prior to Jan. 1, 1958), to be safe under the conditions of their intended use.

Flavor and Extract Manufacturers Association (FEMA)- Organization which sponsored the formation of an independent panel of experts to perform GRAS

assessments and to provide their conclusions to the U.S. Food and Drug Administration, the food and flavor industries, and the public to provide for the assessment of flavor ingredients as GRAS under the Food Additives Amendment to the U.S. Federal Food, Drug, and Cosmetic Act.

FDA/FEMA GRAS Statement (Sometimes "Ingredient Statement"): A document certifying that all flavor ingredients in this product are listed as being generally recognized as safe on a reliable published industry association list and/or approved for use in a regulation of the FDA. This document helps assure the Purchaser that the ingredients are approved for use in foods by the FDA or qualified experts associated with the FDA (*i.e.*, FEMA).

FDA Ingredient Declaration (Sometimes called "Label Declaration"): A document listing all components of an ingredient as required per FDA food labeling regulations.

Ingredient Specification (Sometimes "Certificate of Analysis," "Product Specification", "Technical Specification", "Product Information"): A document containing physical data (color, odor, appearance, refractive index, specific gravity, flashpoint, etc.), as well as storage and/or shelf life information and quality or purity information. It also may contain relevant information about the ingredients as well as microbial and/or allergen information (see other definitions for microbial and allergen statements). For example, a Label Statement such as "All flavor ingredients contained in this product are approved for use in a regulation of the FDA". This document is primarily used to identify the material received.

Microbial Certificate of Analysis (or Microbial Statement): A document indicating microbial content or measurement. The information sometimes appears on the Certificate of Analysis (CoA) or Technical Information sheet, or it may appear as a stand-alone Microbiological Statement. Several examples are listed in order to help understand the wide variety of documents (or statements) received from vendors;

- If an analysis has been run, one may receive information that includes one or more of the following test information; water content, total plate count, Yeast, Mold, Coliforms, Staphylococcus aureus, Listeria, E. coli and Salmonella analyses.
- Additional statements include examples such as "The product listed below is deemed microbiologically non-sensitive upon review by a qualified microbiologist …" **or** "The items listed below are not considered 'micro-sensitive;' therefore, they do not require micro-testing."
- Supplier may indicate that they do not perform "micro-testing" since all of their ingredients are synthesized using food grade ingredients and the end product is a chemical ingredient.

PHA – Preliminary Hazard Analysis: Methodology for analyzing potential problems during the development cycle to take actions to overcome these issues, thereby enhancing reliability through design. Used to identify potential failures, determine their effect on the operation of the product, and identify actions to mitigate the failures.

Product Component: Product components comprise those materials which are directly added to a product for a specific functional purpose (excluding tobacco). The term Product Component is intended to include the terms "additives, ingredients and non-tobacco components" which are sometimes used for regulatory disclosure and communication purposes. A product component can be a pure chemical or a mixture of chemicals.

Technology: The method and material used to achieve a commercial or industrial objective.