Altria
Altria Client Services

Product Integrity
Toxicological Evaluation Framework Overview

Table of Contents

1 Introduction

Operating companies of Altria Group are currently manufacturing and developing consumer products in various product platforms. Technologies, processes, and materials used in products or product prototypes are evaluated by Product Integrity. Such evaluation serves as the mechanism for providing recommendations regarding the suitability for use of product components, packaging or manufacturing materials, processes, integrated technologies and integrated product designs, including those that are new or serve as replacements for those currently in use.

Products in different categories may vary in their risk profile, in the degree of toxicological information available for the products and components, as well as the in the regulatory status of the products and components. Product Integrity Acceptability Evaluation Guidelines will be developed on a platform specific basis to describe the basic approaches used for an evaluation.

2 Purpose

The purpose of this document is to describe a consistent framework within which Product Integrity applies acceptability evaluations across various product categories. The concepts in this framework enable evaluation of a diverse range of products such as cigarettes where toxicity issues are high, where there is limited information available and no regulatory guidance, to foods where adherence to existing regulation provides an assurance of safety.

3 Framework

The framework for application of the Product Integrity evaluation is shown in Attachment 1.

Based on the relevant scientific and regulatory principles, considerations, and recommendations, as well as current toxicological knowledge, a core battery of work has been established for potential use in toxicological evaluations. This battery includes activities such as: Review of the history of use in similar type products and food use status, review of current scientific literature, analysis of potential chemicals generated by volatilization or pyrolysis, review of chemical profile for smoke constituents, genotoxicity assays in bacterial and mammalian cells, and appropriate animal toxicity studies (*e.g.*, rodent smoke inhalation). All, or parts, of this battery may be used in performance of an evaluation.

As noted above, specific requirements and considerations which may be unique to a specific product platform are outlined in the appropriate Product Integrity platform-specific guideline document.[1]

The recommendation process begins with an assessment of exposure to the material by ingestion or inhalation. If exposure is not possible or very unlikely, a recommendation may be made solely based on this lack of potential for exposure, the literature available and the history of use according to requirements detailed in the platform-specific guidelines.

If it likely that there is exposure, the Generally Recognized as Safe (GRAS)/ Food Additive status of the material or component is reviewed, as well as, the probability of the material or component being burned in normal use (*i.e.*, lit-end product use). For items that are considered acceptable food additives (*e.g.*, GRAS) and would not be expected to be burned as a consequence of use, the requested use (application and level) is compared to any established use limitations for food products (*i.e.*, use level or function). An acceptability determination may then be made based on existing data and precedent, or completion of additional testing to support use. Alternatively, the material will not be used.

For those materials which are not considered acceptable for food use or may be used in situations where they may be expected to be burned the next step is to determine if there are sufficient data available to make a decision based on the requirements in the platform-specific guidelines. Some considerations used for this decision are listed in Box 1 in Attachment 1. Factors may include existing precedent or limitations established by tobacco product authorities, or existing literature data describing studies where the material is tested in a situation similar to the proposed use. If sufficient data are deemed to be available to support an evaluation, a decision may be made on the basis of existing data alone. If data are deemed to be insufficient, additional testing may be conducted to support the evaluation process. For items not burned this would include following the internal GRAS review process.[2] For burned items the amount and type of testing depends on two factors:

1. History of use
2. Level of use.

---

[1] Product Integrity Review and Toxicological Evaluation Guideline-Smokeless Tobacco Products: Test Articles, Prototypes, and Products
Product Integrity-Review and Toxicological Evaluation Guideline-Cigarette Products
Product Integrity Review and Toxicological Evaluation Guideline-Oral Exposure: Test Articles, Prototypes and Products Intended as Foods

[2] Process for Completing GRAS Determination-Currently in Draft Format – 9/17/08, E.J. Copeland

The evaluation considers any relevant known toxicity concerns related to the neat material and, where appropriate, the potential for toxicants to be formed during the burning process. For situations which have no established precedent for use in burned tobacco products, the suggested testing regimen is based on a tiered use level approach using calculations developed from the FDA Redbook for foods[3] (US FDA, 2000) and described in the platform-specific guidelines. For situations where there is some precedent for use but the requested levels may exceed those historically used or those described by the literature, a modified testing battery may be applied. The selection of this battery is based on current understanding of the sensitivity of the *in vivo* and *in vitro* assay systems typically used for tobacco product evaluations. In both cases progressively more testing is done for the higher exposure levels. This tiered approach is intended to increase the probability of detecting a potentially toxicologically relevant change in the product attributable to the design change under consideration (*e.g.* use of a new ingredient or product design).

For items that do not fit into the level paradigm, *i.e.*, non-quantifiable changes or design changes, the amount and type of testing will be determined on a case by case basis.

In any case, the data are reviewed and when it is established there are sufficient data to make a decision, a recommendation will be rendered.

4 Scientific Judgment

The evaluation is an iterative process which will frequently utilize data obtained from multiple sources of both chemical and biological nature. Such a process relies upon the expert judgment of properly trained and experienced reviewers to evaluate the existing data and formulate rational conclusions. Consideration will be given to relevant available data based upon the scientific strength of the results and the appropriateness of the testing methodologies used. Views, conclusions and approaches may change from time to time as new information becomes available. Generally, no single factor *(e.g.*, report in the literature, endpoint or assay result) determines the overall recommendation, and the factors considered are not scored mechanically by adding pluses and minuses; but are judged holistically.

5 Guideline Evolution

We consider the current approaches used in this framework and in the related guidelines to be consistent with approaches used for other consumer products. Product Integrity will

[3] US FDA. Office of Food Additive Safety Redbook 2000. (2000) *Toxicological Principles of the Safety Assessment of Food Ingredients*. Updated October 2001 & November 2003. US Food and Drug Administration, Washington DC.

continue to evolve the evaluation program by developing and incorporating new approaches and methodologies when, in our judgment, the science dictates this.

6 Revision History

Revision #	Date	Reason for Revision
01	11/18/08	Original-DRAFT

Attachment 1: Decision Making Flow Diagram