Altria

Altria Client Services

Toxicological Evaluation Guideline

Tobacco Product Packaging Materials

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1 Introduction

A toxicological evaluation serves as the mechanism to document and communicate toxicological assessments regarding the suitability for the intended use of product components, packaging, manufacturing materials, processes, technologies and product designs. This guideline applies to the evaluation of packaging materials for tobacco products as defined by the Family Smoking Prevention and Tobacco Control Act. The Toxicological Evaluation Framework Overview describes the elements of a toxicological evaluation while this guideline applies this overall framework to Packaging Materials for Tobacco Products.

This document, and the overarching decision-making framework, are intended as guidance only and do not establish rules. The guidance represents sound and up-to-date approaches, but assessments may be conducted differently than outlined here for a number of reasons. For example, novel product configurations may require unique evaluation approaches. With this in mind, 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. The Toxicologist(s) 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.

2 Purpose

The purpose of the toxicological evaluation of packaging materials is to provide a basis for assessing whether the packaging construct has the potential to result in an increase in the toxicity of tobacco products compared to the inherent toxicity of currently marketed tobacco products. A packaging construct is a specific arrangement of distinct materials comprising the complete package and may include substrates (*e.g.,* materials that serve as the surface to be printed), inks, adhesives, promotional items, or other components of the product packaging as appropriate. Since different tobacco products may have different packaging constructs, the requirements for each evaluation will be grounded in the intended use of the material to be evaluated. The requirements for similar materials, therefore, may differ between product platforms.

3 Scope

This guideline is intended to address evaluations of packaging materials across tobacco product platforms and intended uses.

Specific items for evaluation include, but are not limited to:

Cigarette and e-Vapor product paperboards (*e.g.*, inner frame, pack, box, cartons)

e-Vapor product blister/pouch

Oral/Smokeless tobacco product container components (*e.g.*, polypropylene, cardboard)

Over wrap films (*e.g.*, cigar wraps, cigarette pack over wrap, log wrap)

Packaging inks (*e.g.*, cigarette packs, cigar packs, side labels for oral/smokeless tobacco containers, e-vapor product pack)

Coatings, lacquers, varnishes

Packaging adhesives (does not include adhesives found on the cigarette/cigar rod)

Promotional materials

4 Evaluation Rationale

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. Generally, no single factor (*e.g.*, report in the literature, endpoint or assay result) is unduly weighted, and the factors are not scored mechanically by adding pluses and minuses; they are judged holistically. These factors are taken into account throughout the evaluation with the goal of producing an objective appraisal of the available data.

Since most evaluations will use data obtained from multiple sources of both chemical and biological relevance, the toxicological evaluation will consider relevant available data including the scientific strength of the results and the appropriateness of the testing methodologies. The weight of evidence approach, where a single integrative decision is made after assessing all of the individual lines of evidence, is consistent with the approach incorporated into other health assessment guidelines including the US Environmental Protection Agency (EPA) Guidelines for Carcinogen Risk Assessment (EPA, 2005). The weight of evidence approach addresses not only possible effects of the chemical or design, but also the conditions under which such effects may be expressed.

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. Weight of evidence relies upon the expert judgment of a properly trained and experienced reviewer to evaluate the data and formulate rational conclusions.[1]

While there are no regulations specific to tobacco product packaging, the existing United States Food and Drug Administration (FDA) and European Commission (EC) regulations serve to inform the toxicological evaluations of tobacco product packaging. For packaging materials and ingredients which are regulated as food additives by relevant regulatory agencies (*e.g*., FDA, EC) 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 will be based on intended use including product platform, location of material with respect to the finished consumable product, intended market for the product (*e.g*., United States, European Union, Japan etc.), as well as any other information, including analytical data, deemed necessary to formulate a recommendation.

5 Evaluation Fundamentals

5.1 Intended Use

Evaluations addressed by this guideline include assessment of levels of various chemical constituents and parameters in packaging materials 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), the FDA, the EC and the U.S. National Cancer Institute (NCI). Evaluations may also include analytical testing to assess the propensity for the packaging material to contribute to the inherent toxicity of the product whether by volatile contribution or physical migration.

The toxicological evaluation procedure is grounded in the intended use of a packaging material; therefore, it is imperative to identify how specifically the material will be used and, in effect, how the material may impact the product. A flow chart has been prepared to aid in this decision-making process (Figure 1). The level of detail is a matter of scientific judgement and discretion using the decision-making framework and this guideline. Based on various 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. These activities may include a review of history of use and food approval status, review of current scientific literature, analysis of potential chemicals generated by volatilization or pyrolysis,

[1] Personnel Credentialing Guideline for Toxicological and Product Quality Incident Evaluation

regulatory guidance issued by regulatory agencies for foods and applied to tobacco products including migration analysis.

5.2 Using Food Regulation as Guidance

While tobacco products are not subject to the existing regulations around food packaging, the science behind the regulations is applicable nonetheless. It is therefore reasonable to apply food packaging regulations as a general safety standard to packaging materials for tobacco products. Understanding that food packaging regulations may vary widely between regions and countries, applicable food regulations from the country in which the product will be marketed should be considered in the review of the packaging material. In the case of oral/smokeless tobacco products, the intended use of the packaging materials and their potential contribution to the product parallels that of foods. In the case of combustible products, it is possible to follow similar guidance from the food regulations and then further extrapolate using basic toxicological principles to consider the possible impact of packaging materials on the combustible products.

5.3 Regulatory Status

The United States (US) and European Union (EU) differ fundamentally in approach to regulatory concepts. The FDA and EC are the regulatory agencies responsible for providing food contact materials regulations in the US and EU, respectively. The FDA regulatory approach considers risk and dietary exposure to determine the level of toxicological testing required prior to use as a food contact material. Analytical testing and extrapolation can be used to demonstrate anticipated exposure to a component would be below levels which would incite toxicological concern. Conversely, the EC approach is to consider toxicological data for any food contact material regardless of the anticipated exposure level. The toxicological data is then reviewed to create a positive list of materials for use. Therefore, the amount of data required to prove safety is dramatically different between the two regulatory bodies.

To evaluate the Regulatory status of tobacco product packaging or a component of tobacco product packaging the following questions may be addressed:

1. Is the packaging material itself the subject of a regulation? Is the supplier able to provide a statement of adherence to a specific regulation? Has the supplier provided a statement adequate for the intended market?

2. Is there a barrier to physical migration (defined in next section) between the packaging material or component and the finished consumable product?

3. Are the components of the packaging material the subject of a specific regulation (*e.g.*, 21 CFR or E number) or are they GRAS for addition to food?

4. Is it possible to demonstrate "no migration" of the components of the packaging material into the finished consumable product (*i.e.,* by migration modeling or analytical migration testing)?

The definition of a food additive by both the FDA and the EC indicate that any packaging material is a food additive unless it is not reasonably expected to become part of the product (*vide infra*). In order to establish that a packaging material or component of a packaging material is not a food additive, it must be demonstrated that the components do not migrate. The "no migration" exemption, for the FDA, is satisfied when it can be shown that a packaging component may be present in the finished consumable product at less than 50 ppb (wt/wt). In the EU, the EC has defined overall and specific migration limits for packaging components. These are discussed further in Section 5.4.1.

Definitions of food additives

FDA: Section 201(s) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 USC 321) defines a food additive as "any substance the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food (including any substance intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food; and including any source of radiation intended for any such use)" and Section 409 (21 USC 348) requires that food additives be the subject of a regulation or a food contact notification.

EC: Article 3 of Regulation 1333/2008/EC defines a food additive as "any substance not normally consumed as a food in itself and not normally used as a characteristic ingredient of food, whether or not it has nutritive value, the intentional addition of which to food for the technological purpose in the manufacture, processing, preparation, treatment, packaging, transport or storage of such food results, or may reasonably expected to result, in it or its by-products becoming directly or indirectly a component of such foods."

5.4 Evaluation Model

When considering the questions posed in the flowchart (Figure 1), the following information will inform the decision.

5.4.1 Barriers to Physical Migration

There are very few prescriptive barriers to physical migration, also known as functional barriers, defined by FDA. Glass and aluminum as well as sufficiently thick polymers, such as 1 mil polyethylene-teraphthalate (PET), may be considered functional barriers (Guidance for Industry: Use of Recycled Plastics in Food Packaging: Chemistry Considerations – August 2006). It is possible to demonstrate that a material is a functional barrier to specific migrants, but this requires migration analysis using the specific packaging material of interest and any migrants that may be associated with that

packaging or any packaging material further removed from the finished consumable product. In short, this means that only the materials described above are *de facto* functional barriers, while it must be demonstrated that other materials are functional barriers to the specific migrants of interest.

The EC does not define prescriptive functional barriers like the FDA. Therefore, the presence of a functional barrier must be demonstrated through migration analysis using the specific packaging material of interest and any unauthorized substance that could be a migrant. A plastic layer is considered a functional barrier when migration of any unauthorized substance is undetectable with a detection limit of 10 ppb (Guidance document on fat reduction, functional barrier concept, phthalates and primary aromatic amines – JRC 2011).

Once it is determined that there is a functional barrier to physical migration between the packaging material being evaluated and the finished consumable product, it is important to consider the product platform on which the material is to be used, and the flow chart may be utilized to aid with the formulation of a recommendation of the material.

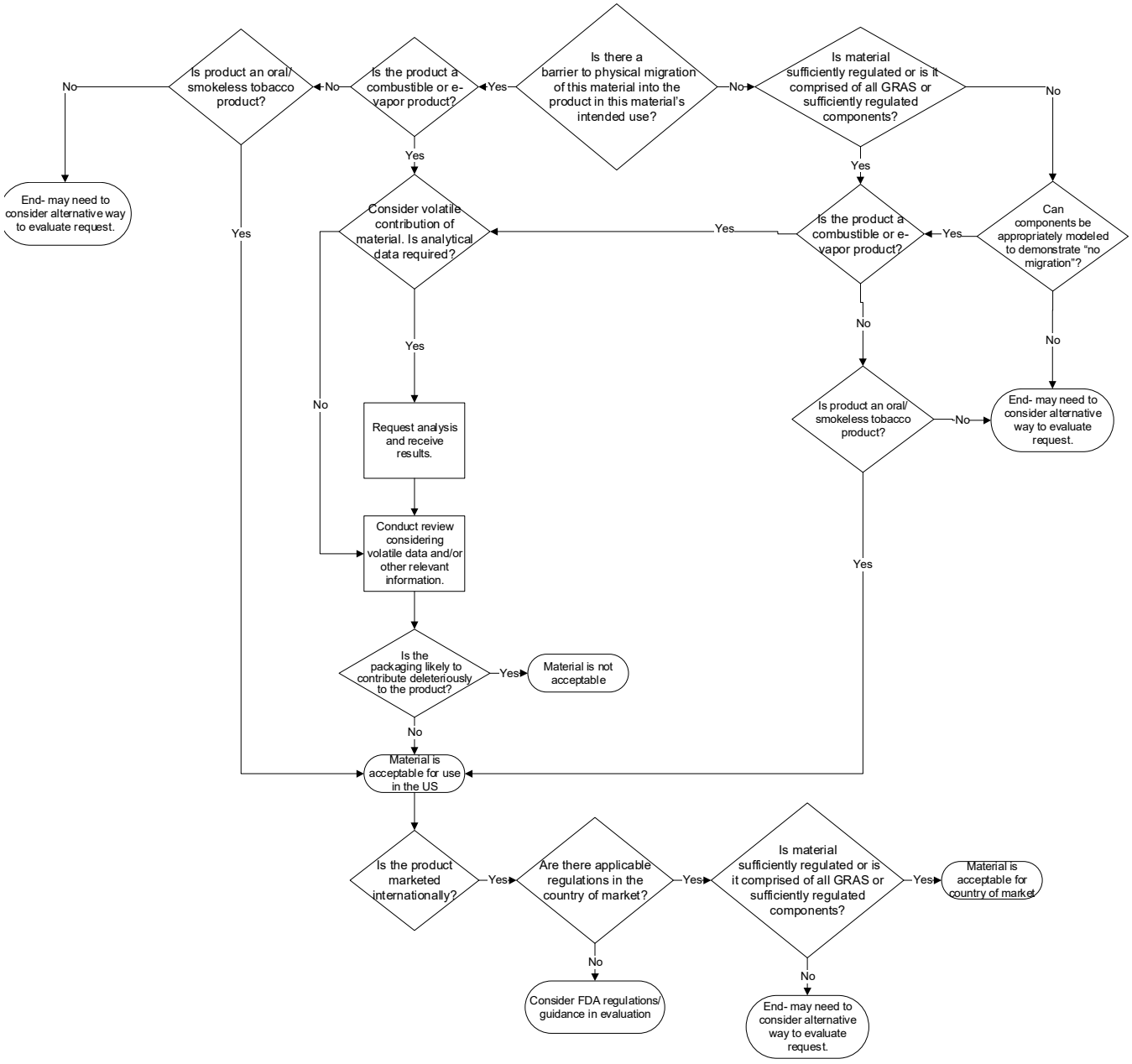

Figure 1. Flowchart of Packaging Material Evaluation Process

5.4.2 Contribution of Volatile Materials to Combustible Tobacco Products

Since the intended use for cigarettes, cigars, and pipe tobacco is to be burned, the toxicological evaluation of packaging materials associated with these types of products must account for the potential of volatile materials from the packaging to be liberated during packing, shipping, and storage of the product and subsequently become part of the tobacco product with the potential to contribute to the toxicity of the smoke. Purge and trap analysis is used as a method to semi-quantitatively determine what, if any, contribution a packaging material may make in a worst-case scenario. Any identified compounds will be assessed using methodology previously described in Section 4.

5.4.3 Evaluation of Packaging Materials when there is no Functional Barrier

When evaluating packaging materials in the absence of a functional barrier, information regarding chemicals and their status as food additives specific to the country in which the product will be marketed should be considered. If appropriate, a statement of compliance with relevant regulations should be obtained from the supplier of the packaging material. For domestically marketed products, the FDA Title 21 of the Code of Federal Regulations (21 CFR) will provide the information. Where applicable, a statement of compliance to a relevant 21 CFR (*e.g.*, 175.105 – Components of Adhesives) should be obtained. For products marketed in the EU, a statement of compliance with the framework regulation 1935/2004/EC should be obtained unless the packaging material of interest is covered under specific measures by the EC or individual member states. For example, plastic materials and articles are covered under Regulation 10/2011/EC.

This guideline, in the absence of guidance from regulatory agencies, is not so prescriptive as to infer that to allow use of a packaging material for tobacco products that it must strictly follow the intended use of the material according to 21 CFR or other regulations (*e.g.*, EU). A material's regulation as a food additive may be wholly sufficient.

Occasionally it may be necessary to consider a packaging material as its individual components for the purposes of determining its acceptability for use. This is common with printing inks as inks, *per se*, are not regulated as discreet entities by the FDA or the EC. It may be possible to demonstrate that all components of an ink are GRAS, or are sufficiently regulated as food additives by the FDA or the EC. Because the FDA defines a threshold of migration in Guidance for Industry: Preparation of Premarket Submissions for Food Contact Substance: Chemistry Recommendations, it may be possible to demonstrate that migrants do not migrate at levels above a threshold of migration. This "no migration" limit is generally 50 ppb but may be as low as 10 ppb. For the EU, the framework regulation defines an overall migration limit (OML) of 60 ppm for substances migrating into food. The OML is applicable unless a specific migration limit (SML) is defined for a particular migrant. SMLs are defined in specific measures regulations, such

as the plastics regulation 10/2011/EC. Compliance with the migration limits defined by the EC or the "no migration" exemption defined by the FDA may be reached by analytical testing under prescribed conditions or by modeling migration using commercially available software. By definition, if a chemical does not migrate, it is not a food additive as discussed previously in Section 5.2.

6 Guideline Evolution

We consider the evaluation approach and current assays used in our guidelines to be consistent with the state of the art for tobacco products and consistent with approaches used for other consumer products. However, we will continue to evolve the evaluation procedure by developing and incorporating newer methodologies and approaches that we deem relevant to the evaluation process. With this perspective, it is expected that the methods and approaches used will vary over time as we continue to improve our evaluation procedure.

7 Revision History

Revision #	Date	Reason for Revision
01.0	09/27/2019	Original Issue, Business need.
01.1	12/19/19	Updated DCN to reflect new category of Product Integrity (034) and added effective date.