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Given the above, all interested persons should refer to the Federal Food, Drug, and Cosmetic Act, and its implementing regulations, as well as guidance documents and webinars prepared by FDA, for information on FDA's tobacco authorities and regulatory framework. This document does not bind FDA in its review of any tobacco product application and thus, you should not use this document as a tool, guide, or manual for the preparation of applications or submissions to FDA.



MEMORANDUM

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From: Brian E. Erkkila, PhD
Biologist
Division of Nonclinical Science, Office of Science

Through: Phil Yeager, PhD, DABT
Senior Toxicologist
Division of Nonclinical Science, Office of Science

Kimberly Benson, PhD
Director
Division of Nonclinical Science, Office of Science

To: File

Subject: SE Review: Evaluation of Multiple Ingredient Changes

Brian E. Erkkila -S
Digitally signed by Brian E. Erkkila -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=0013767881, cn=Brian E. Erkkila -S
Date: 2015.02.09 10:50:12 -05'00'

Digitally signed by Philip Yeager -S
Date: 2015.02.09 10:52:11 -05'00'

Kimberly A. Benson -S
Digitally signed by Kimberly A. Benson -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300148295, cn=Kimberly A. Benson -S
Date: 2015.02.09 10:58:49 -05'00'

Purpose

This memo reflects the Division of Nonclinical Science’s current thinking on the currently published literature and how these published studies inform our evaluation of the toxicological impact of multiple ingredient changes.

Background

The Federal Food, Drug, and Cosmetic Act (FD&C Act) provides a pathway for tobacco product manufacturers to introduce new tobacco products into interstate commerce by establishing that they are substantially equivalent (SE) to appropriate predicate products under section 905(j) of the FD&C Act. Section 910(a)(3)(A)(i-ii) of the FD&C Act provides that a substantially equivalent tobacco product “(i) has the same characteristics as the predicate tobacco product; or (ii) has different characteristics and the information submitted ...demonstrates that ...the product does not raise different questions of public health.” During the scientific review of SE Reports of tobacco products (i.e. cigarettes) by the CTP’s Office of Science, a few questions have been raised about evaluating the toxicological impact of ingredient changes between new and predicate products. A unique aspect of tobacco product evaluation is that such review must consider that cigarette use often involves combustion and the ultimate pyrolysis of ingredients. This is in contrast with the evaluation of oral tobacco products, where relevant information on the toxicity of an

SE Review: Evaluation of Multiple Ingredient Changes

ingredient (FDA/FEMA GRAS designation), can give insight into the potential effects of addition of that ingredient to a new tobacco product. In an effort to maintain the particular desired flavor profile in what is essentially a variable agricultural product, numerous ingredients are often added or changed in quantity by a manufacturer. This has been seen over the course of numerous reviews of submitted SE Reports to date.

In the SE Reports that OS has reviewed to date, manufacturers have at times presented their justifications that the changes in ingredients/additives between their new and predicate products do not raise different questions of public health by referencing publications, which examine experimental cigarettes with varying ingredient profiles. It is important to note that most of these published studies are designed to examine flavorings that in fact are being added to new products in the SE Reports; however, these studies are nearly always using the flavorings in different quantities in the new or predicate products in the SE Reports. In addition, these studies from the published articles nearly always compare experimental cigarettes that have been constructed with multiple differences in ingredients/additives/flavorings, therefore they are actually studies of combinations of changes and not reflective of the change that is being proposed in the SE Reports that are submitted to CTP. As a substantial equivalence evaluation relies on a comparison between only the new and predicate products, the challenge lies in determining if these ingredient changes impart a modification which causes the new product to raise different questions of public health. The published studies that are referenced have been conducted to look at multiple changes at a single time and do not examine single ingredient changes in such a way that potential ingredient-specific effects can be isolated and diminishes the studies utility in supporting a change of ingredient X to a level of Y mg/g, for example.

Substantial Equivalence Review: How does the currently published literature inform FDA's evaluation of the toxicological impact of multiple ingredient changes?

There have been several lines of investigation that have attempted to make the concurrent examination of multiple ingredients workable. One such method examines multiple ingredients in a matrix (Baker, 2004 a,b,c; Roemer et al., 2002). Mainstream smoke from experimental cigarettes with differing levels of many common ingredients (flavors, humectants, solvents, processing aids, etc.) can be evaluated in chemical and toxicological assays. The use of a combination of ingredients in research cigarettes could provide information concerning any potential interactions between product ingredients, but only if they are used in similar levels and ratios to the new and predicate products in question. The interactions of these chemicals could be *additive*, that is the effect of the multiple chemicals is equal to the sum of the individual ingredients. For instance the cholinesterase inhibition by multiple organophosphate insecticides is generally additive (Eaton and Gilbert, 2008). Alternatively there could be a *synergistic* effect between constituents, in which the combined effect of several chemicals is greater than the sum of the chemicals alone. For example, carbon tetrachloride and ethanol given in tandem are considerably more hepatotoxic than the agents given independently (Eaton and Gilbert, 2008). *Potentiation* may cause a typically inert chemical to have a toxic effect, such as the much greater hepatotoxicity of carbon tetrachloride in the presence of isopropanol (Eaton

SE Review: Evaluation of Multiple Ingredient Changes

and Gilbert, 2008). Additionally there could be one of many forms of antagonism, in which the toxicity of an agent is decreased by other components of the mixture. In a mixture like cigarette smoke, with thousands of components, it is likely that some or all of these interactions are occurring at once, resulting in innumerable permutations (Eaton and Gilbert, 2008). A review by Kortenkamp and colleagues found substantial evidence for mixture effects well below the agents no observable adverse effect levels (NOAEL) (Kortenkamp et al, 2007). Therefore, studies of research cigarettes with “similar” ingredient mixtures that do not isolate ingredient-specific effects may provide some information regarding the comparative toxicities of experimental cigarettes; they do not provide sufficient information concerning the toxicological impact of individual ingredient changes. Specifically, in any SE Report, when CTP is evaluating scientific evidence submitted in support of the claim that proposed modifications do not raise different questions of public health, it is important that the data provided be relevant to the actual changes between the new and predicate products.

The production of experimental cigarettes with individually altered ingredients allows for both the creation of a “dose-response” relationship as well as the creation of experimental products with greater exaggeration of ingredient concentrations (Roemer et al., 2010; Coggins et al., 2011*; Gaworski. et al., 2011*). In such studies the influence of individual ingredient levels on smoke chemistry, cytotoxicity, genotoxicity and mammalian inhalation studies may be examined. While this approach generally allows for more unambiguous results, even with a study with this design, toxicological evidence must be evaluated to ensure that the bioassays used are sensitive enough to detect meaningful differences, that the measured toxicity of any dose-response relationship does not lay at the upper asymptotic portion of the curve where increases will be difficult to detect, and that the results are derived from a sound rationale and experimental approach.

Lastly, the most applicable data to evaluate the potential impact of differences in ingredients would be a direct comparison between the new and predicate products in question. For example, evidence indicating similar HPHC levels in smoke, comparable results in properly conducted *in vitro* bioassays and no significant differences in toxicological endpoints *in vivo*, would be the most compelling evidence that ingredient changes do not raise different questions of public health. At present, references to open-literature articles authored by industry are the most common scientific evidence provided by the applicant in SE Reports and often the publications refer to scientific results performed by the applicant and/or others. This approach is not a typical submission format for FDA review. In other FDA Centers, long-established policies require submission of GLP studies that include the line-listing data underpinning study results and conclusions and that include the details of study protocol and conduct. The most convincing data for SE evaluation would include such details and allow the reviewer to reconstruct study conclusions from line-listing data between the new and predicate products, if necessary. However even in those other Centers, all information submitted by an applicant is thoroughly reviewed and given due scientific consideration to the applicability of the information to the question at hand. CTP will always analyze all information submitted by the applicants and determine if it is scientifically appropriate for answering the specific scientific question. This memo reflects current thinking about the common practice

SE Review: Evaluation of Multiple Ingredient Changes

detailed above and that citing references of publications that evaluate multiple changes at one time, in many cases, is not scientifically appropriate for addressing specific changes in ingredients.

In Summary:

The Division will continue to assess the applicability of referenced literature in SE Reports on a case-by-case basis, dependent on the changes proposed to the new product in the SE Report. The Division is also currently writing summary reports for the published references that are commonly used in the SE Reports to support the manufacturers' assertions of 'no different questions of public health'. These reviews, which will be kept within the Division as additional memos to file, will critique the methodology and findings, as is best possible with a literature report devoid of such things as line listings, raw data, full study reports. These review memos will also discuss situations in which it is believed the studies could be supportive of a claim of SE within a Report, and those situations in which the study would not be supportive. They will also set forth common language that can be used by all reviewers for any toxicology SE reviews that include the specific references as justification for the proposed finding of SE for a new product.

Baker, R.R., Pereira da Silva, J.R., and Smith, G. (2004a). The effect of tobacco ingredients on smoke chemistry. Part I: Flavourings and additives. *Food and Chemical Toxicology*, 42S, S3-S37.

Baker, R.R., Pereira da Silva, J.R., and Smith, G. (2004b). The effect of tobacco ingredients on smoke chemistry. Part II: Casing ingredients. *Food and Chemical Toxicology*, 42S, S39-S52.

Baker, R.R., Massey, E.D., and Smith, G. (2004c) An overview of the effects of tobacco ingredients on smoke chemistry and toxicity. *Food and Chemical Toxicology*, 42S, S53-S83.

*Coggins, C.R.E., Wagner, K.A., Werley, M.S., and Oldham, M.J. (2011). A comprehensive evaluation of the toxicology of cigarette ingredients: carbohydrates and natural products. *Inhalation Toxicology*, 23(S1), 13-40.

Eaton DL and SG Gilbert, 2007. Chapter 2. Principles of Toxicology. Casarett and Doull's Toxicology: The Basic Science of Poisons. Ed. C. Klaussen, McGraw Hill Professional, New York, NY, pp. 11-44.

*Gaworski, C.L., Oldham, M.J., Wagner, K.A., Coggins, C.R.E., and Patskan, G.J. (2011). An evaluation of the toxicity of 95 ingredients added individually to experimental cigarettes: approach and methods. *Inhalation Toxicology*, 23(S1)

Kortenkamp, A., Faust, M., Scholze, M. and Backhaus, T. (2007). Low-level Exposure to Multiple Chemicals: Reason for Human Health Concerns?. *Environmental Health Perspectives*, 115, 106-114.

Roemer, E., Tewes, F.J., Meisgen, T.J., Veltel, D.J., and Carmines, E.L. (2002). Evaluation of the potential effects of ingredients added to cigarettes. Part 3: In vitro genotoxicity and cytotoxicity. *Food and Chemical Toxicology*, 40, 105-111.

*These collaborators completed a rather extensive series of studies in 2011 examining the impacts of single ingredients on tobacco product smoke chemistry and toxicology