The attached document represents CTP's then-current thinking on certain aspects of tobacco regulatory science. The information contained herein is subject to change based on advances in policy, the regulatory framework, and regulatory science, and, is not binding on FDA or the public. Moreover, this document is not a comprehensive manual for the purposes of preparing or reviewing tobacco product applications. FDA's review of tobacco product applications is based on the specific facts presented in each application, and is documented in a comprehensive body of reviews particular to each application.

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

Date: March 17, 2015

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Date: 2015.05.11 14:11:54 -04'00'

To: File

Subject: SE Review: Evaluation of estimated HPHC Impact of Single Ingredient (saccharides) Pyrolysis

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## Purpose

This memorandum reflects the Division of Nonclinical Science's current thinking on how pyrolysis of a single ingredient (saccharides) may impact the estimated HPHC levels, such as carbon monoxide (CO), acetaldehyde, acrolein, and formaldehyde.

## 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 by the CTP's Office of Science (OS), 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. 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. These published studies 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 (Baker, 2004 a, b, c; Roemer et al., 2002). For more details, see "Memo to File – Ingredient Differences – Literature Support".

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, including HPHC levels in smoke, properly conducted *in vitro* bioassays and toxicological endpoints *in vivo*. However, most SE Reports do not provide these data. While FDA currently does not require manufactures to provide HPHC data in an SE Report, such information can and has been supplied in response to a deficiency outlined in a Scientific A/I letter. Deficiencies can identify that reporting of a subset of HPHCs for the new and predicate products can address the issue of whether a specific change between the products raises different questions of public health. Published scientific literature that addresses how ingredient changes would potentially influence HPHC levels is very limited. Without measuring the actual HPHC levels, it is difficult to accurately estimate how the changes in ingredient types and quantities in the new products would impact the overall consumer exposure to HPHCs. The method discussed below provides a semi-quantitative approach for evaluating the potential impacts of ingredient changes and subsequent levels of pyrolytic products produced by combustion, when the empirical HPHC data for a new and predicate product is not provided in an SE Report.

**Substantial Equivalence Review: Estimation of HPHC impact from pyrolysis of single saccharide ingredients**

Baker *et al.* developed a system that simulates cigarette combustion conditions to measure the formation of pyrolysis products of tobacco ingredients (Baker, 2005 a, b). In these studies, a two-stage ramped temperature program was used that simulated the burning conditions of a smoldering cigarette: an initial heating to 300 ºc, then increased the temperature to 900 ºc and held at this temperature. In Baker 2005b, the pyrolysis products were determined using a GC/MS system. However, for low molecular weight pyrolysis products that were not detected by a GC/MS system, such as CO, formaldehyde, acrolein, a Fourier-transform infrared spectrometer (FTIR) system was used (Baker 2005a). In Baker 2005a, the authors semi-quantified the pyrolytic products and normalized them as µg/mg ingredient. These data provided an easy way to convert the increases of ingredients to the potential generation of HPHCs. In this memorandum, only data from Baker 2005a are used. Thirteen saccharide tobacco ingredients (4–30 mg of sample) have been studied using the FTIR system (Baker, 2005a). The yields of low molecular weight pyrolysis products were semi-quantified and normalized to the weight of the saccharides (see Table 1 below).

Table 1 *:

Total yields of pyrolysis product normalised to weight of saccharide (μg $mg^{-1}$)

| Pyrolysis product | Sugars | | | | | | | Cellulosics and starch | | | | Gums | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Fructose | Glucose | Brown sugar | White sugar | Cane sugar | Invert sugar | Molasses | Cellulose fibre | HPC[a] | CMC[b] | Starch | Acacia gum | Xanthan gum |
| CO | 0.28 | 0.22 | 0.20 | 0.36 | 0.39 | 0.20 | 0.28 | 0.20 | 0.70 | 0.47 | 0.59 | 0.43 | 0.49 |
| $CO_2$ | 3.3 | 3.4 | 4.8 | 4.0 | 4.5 | 4.5 | 5.3 | 3.0 | 6.1 | 6.3 | 2.4 | 7.1 | 7.8 |
| Methane | 0.007 | 0.005 | 0.004 | 0.006 | 0.005 | 0.004 | 0.007 | 0.004 | 0.01 | 0.007 | 0.005 | 0.01 | 0.009 |
| Water | 1.1 | 0.89 | 1.3 | 0.71 | 0.65 | 0.58 | 1.2 | 0.79 | 1.7 | 1.8 | 0.93 | 1.0 | 1.3 |
| Acetic acid | 1.2 | 0.63 | 2.3 | 1.9 | 2.5 | 2.7 | 2.5 | 0.71 | n.d. | 1.8 | n.d. | 2.5 | 3.0 |
| Formaldehyde | n.d. | n.d. | 0.61 | 0.37 | 0.16 | 0.33 | 1.2 | 0.21 | 0.91 | n.d. | 0.53 | 0.53 | 0.21 |
| Acrolein | n.d. | n.d. | n.d. | 0.19 | n.d. | n.d. | 1.2 | 1.3 | 1.4 | n.d. | 0.31 | n.d. | n.d. |
| Acetaldehyde | 0.46 | n.d. | 0.11 | n.d. | n.d. | n.d. | n.d. | 0.40 | 1.7 | 0.40 | n.d. | 0.92 | n.d. |
| Ethanol | n.d. | n.d. | 0.64 | n.d. | 0.53 | n.d. | n.d. | 0.70 | n.d. | n.d. | n.d. | n.d. | n.d. |
| Furfural | 1.0 | 0.85 | 2.1 | 1.51 | 1.5 | n.d. | n.d. | n.d. | n.d. | n.d. | n.d. | n.d. | n.d. |

n.d.: not detected.
[a] Hydroxypropyl cellulose.
[b] Carboxymethyl cellulose.

*: Table cited from Baker R, Coburn S, et al., Pyrolysis of saccharide tobacco ingredients: a TGA–FTIR investigation. Journal of Analytical and Applied Pyrolysis, 2005a, 74, 171-180

These results provided a method to semi-quantitatively determine the yield of a subset of HPHCs from pyrolysis of saccharides. For example, based on the data in Table 1, pyrolysis of 1 mg of cellulose fiber generates 0.2 μg of CO, 0.21 μg of formaldehyde, 1.3 μg of acrolein. If there is an increase of 10 mg of cellulose in the new products compared to the predicate products, the estimated increase of CO would be 0.2 μg/mg (of cellulose) x 10 mg = 2 μg. Similarly, the estimated increase of formaldehyde would be 0.21 μg/mg (of cellulose) x 10 mg = 2.1 μg; the estimated increase of acrolein would be 1.3 μg/mg (of cellulose) x 10 mg = 13 μg. Table 2 is generated to better illustrate the estimation of the HPHC change from a hypothetical cellulose increase of 10 mg using the calculations based on the Baker information in Table 1. There are two main components in Table 2. The right side shows the information for several HPHCs considering the hypothetical ingredient addition of 10 mg of cellulose, including Normalized Yield from Table 1, the amount of ingredient increase, estimated HPHC increase (Normalized Yield x the amount of ingredient increase). On the left side, the HPHC levels for the reference 1R4F cigarette were provided based on three different smoking conditions, ISO, Massachusetts, and Health Canada Intense (Counts, 2005). The potential impact of this increase of cellulose on HPHCs is calculated as percentage to HPHC levels of reference cigarette 1R4F containing 0.76 g of tobacco (far right column in Table 2). The Health Canada condition is chosen for comparison in Table 2, because the pyrolysis condition in the Baker study does not dilute (no ventilation) the pyrolytic products and it draws the sample constantly. In this example, 10 mg of cellulose does not affect the yield of CO and acetaldehyde, but increases the yield of acrolein (>10%). By the same token, how the increases of sugars (glucose, fructose, etc.), starch, and gums would potentially impact HPHC levels can be calculated and the estimated yields can be evaluated relative to the yields in HPHCs obtained from a combusted reference cigarette.

Table 2: Estimated yields of pyrolytic products

| | Reference 1R4F * | | | Cellulose | | | |
|---|---|---|---|---|---|---|---|
| | ISO [#] (µg/cig) | MDPH (µg/cig) | HC (µg/cig) | Normalized Yield (µg/mg) [$] | Cellulose Increase (mg) | Estimated HPHC increase (µg) | **% of 1R4F HC** |
| CO | 12200 | 22900 | 30100 | 0.2 | 10 | 2 | **0.007** |
| Formaldehyde | 19.3 | 38.7 | 60.5 | 0.21 | 10 | 2.1 | **3.5** |
| Acetaldehyde | 518 | 1101 | 1448 | 0.4 | 10 | 4 | **0.28** |
| Acrolein | 38.5 | 88.3 | 122.4 | 1.3 | 10 | 13 | **10.6** |

* Data from: Counts, M.E., Morton, M.J., Laffoon, S.W., Cox, R.H., Lipowicz, P.J. (2005). Smoke composition and predicting relationships for international commercial cigarettes smoked with three machine-smoking conditions. Regul Toxicol Pharmacolm, 41, 185-227

[$] Data from Table 1: Baker R, Coburn S, et al., Pyrolysis of saccharide tobacco ingredients: a TGA–FTIR investigation. Journal of Analytical and Applied Pyrolysis, 2005a, 74, 171-180

[#] Smoking conditions defined by the International Organization of Standardization (ISO), the Massachusetts Department of Public Health (MDPH), and Health Canada (HC).

## Caveats

The Baker study (2005a) provided valuable information on the pyrolysis of individual ingredients (saccharides) under a condition that closely simulates cigarette combustion. However, it is worthy to note that there are several caveats associated with this study:

1. Pyrolysis conditions used in the study, even though they mimic cigarette combustion, are different from standard smoke machine conditions (ISO or Health Canada Intense). Therefore, the HPHC yields identified in this study may not fully represent the results from standard smoke machine methods. The authors also noted that the pyrolysis system gave higher estimates of the pyrolytic decomposition than what actually occurs in the burning cigarette. The reason seems to be that the samples remain in the high-temperature region longer in the experimental pyrolysis system than when they are part of the combustion matrix in a burning cigarette, and therefore are subjected to greater decomposition (Baker, 2005 b).
2. The study is semi-quantitative. Therefore, the percentage of change in HPHC yields to the reference cigarettes is only an estimation. DNCS has a memorandum to file titled “Concentrations of HPHCs in tobacco and tobacco smoke”, which identified an increase of 10% or greater in HPHCs as an increase that requires further evaluation (See that memorandum for additional details). Consistent with that memorandum, we recommend that a change in an individual HPHC of greater than 10% requires further evaluation when using the approach described in this memorandum.
3. The study focused on the pyrolysis of 13 individual saccharides. The approach described in this memorandum applies only to these 13 saccharides tested in this study (Baker, 2005 a). In this study, the individual saccharide of interest was pyrolyzed as pure compound. This single compound testing approach allows for the measurement of the pyrolytic products produced from the individual saccharide of interest. Therefore, the potential interactions of constituents, ingredients and

their pyrolytic products were not measured from a cigarette containing a complex mixture of ingredients.

**In Summary:**

Due to the limited scientific literature addressing the impacts of single ingredient pyrolysis on smoke HPHC levels, it is currently difficult to determine if an ingredient change would lead the new product to raise different questions of public health in the absence of applicant submitted HPHC data for the new and predicate products of interest. However, the method discussed in this memorandum provides a relevant, semi-quantitative, straightforward way to estimate the HPHC changes based on the best currently available science. As noted above, the study has certain caveats and limitations and the use of this approach should be considered on a case-by-case basis when this method is applied to an ingredient change in tobacco product reviews.

**References:**

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