

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: April 18, 2014

From: Katherine S. Lovejoy, Ph.D.
Chemist
Division of Product Science, Office of Science

Digitally signed by Katherine S. Lovejoy -S
Date: 2014.04.18 09:21:10 -04'00'

Through: Matthew J. Walters, Ph.D., M.P.H.
Chemistry III Branch Chief
Division of Product Science, Office of Science

Digitally signed by Matthew J. Walters
-S
Date: 2014.04.18 09:26:44 -04'00'

Michael L. Koenig, Ph.D.
Deputy Director
Division of Product Science, Office of Science

Digitally signed by Michael Koenig -S
Date: 2014.04.18 09:36:47 -04'00'

To: File

Subject: Use of Reverse Engineering to Reproduce Tobacco Products no Longer
Manufactured or for which Characteristics are Not Available

Background

The Federal Food, Drug, and Cosmetic Act (FD&C Act) provides a pathway for tobacco product manufacturers to introduce a new tobacco product into interstate commerce by establishing that the product is substantially equivalent (SE) to a product that was on the market as of February 15, 2007 (a predicate product) under section 905(j) of the FD&C Act. In many cases, manufacturers no longer manufacture the predicate product and therefore cannot conduct the appropriate tests to demonstrate substantial equivalence to the new product. In other cases, manufacturers of the new products are not the manufacturers of the predicate products to which they would like to demonstrate substantial equivalence. Some applicants have provided FDA with alternative predicate tobacco products in which specific information and testing has been conducted to "bridge" an alternative predicate tobacco product with the actual predicate tobacco product. Other applicants have submitted theoretical products created with the use of modeling software such as Cigarette Designer 4.1. Another way by which applicants might try to reproduce a predicate product involves the use of reverse engineering or attempting to reconstruct a predicate product based on a detailed study of the characteristics of the original predicate product.

Discussion

Reverse engineering is the process of analyzing known features of an object in order to produce something similar.¹ In the case of a reverse-engineered tobacco product, an applicant would produce a new product after attempting to fully characterize a predicate tobacco product, including manufacturing procedures/protocols, tobacco blend compositions including the grade and purity, ingredients and additives present, physical attributes of the product, and chemical characterization of harmful and potentially harmful constituents in the product.

Reverse engineered tobacco products cannot be used as surrogates for predicate products because tobacco products are complex products, processed according to proprietary protocols into highly engineered products. Because of the complexity of tobacco products, we are not aware of any existing analytical techniques that can fully characterize all of their properties. Instead of post-production analysis, companies ensure a consistent, reproducible product by implementing proprietary processes, process controls, and acceptance criteria. Tobacco manufacturers typically do not share proprietary details of their manufacturing processes and trade secrets with their competitors. The manufacturer of a reverse-engineered product does not have direct knowledge of the manufacturing process for the competitor's predicate product and the differences that arise from this lack of knowledge may have an adverse impact on public health.

Proprietary details, unknowable to follow-on manufacturers, that may affect the public health impact of the final product include variations in the growth, harvesting, curing, processing, and manufacturing of tobacco products. These variables include seed source, field location, soil quality, sunlight levels, temperature, weather, agrochemical application, date and method of harvesting. In addition, storage time and conditions between harvesting and curing, method of curing, duration of curing, quantity and quality of non-tobacco ingredients added, physical processing, packaging type, and bacterial growth before and after processing also give each tobacco product its uniqueness. Tobacco-specific nitrosamine levels are affected by the tobacco type and part of the tobacco plant used in the product, as well as agrochemical application and bacterial growth before, during, and after curing. Likewise, polycyclic aromatic hydrocarbons, which are the products of incomplete combustion of carbon sources, are highly dependent on the curing time, temperature, and heat source. Furthermore, manufacturers frequently combine tobacco leaves from different sources to produce a consistent product from year to year. If there is a fermentation step, follow-on manufacturers will be unable to reproduce the exact conditions of fermentation, including microbes present, temperature, relative humidity, and length of fermentation, because the manufacturers do not have direct knowledge of these variables. These are all variables that cannot be known by follow-on manufacturers.

¹ <http://www.merriam-webster.com/dictionary/reverse%20engineer>

Use of Reverse Engineering to Reproduce Tobacco Products No Longer Manufactured or For Which Characteristics Are Not Available

None of these differences are detectable by analytical methods, but all of them have the potential to adversely affect public health.

Because the differences between a predicate product and a reverse engineered product cannot be adequately characterized with appropriate analytical technology, a submission requesting a finding of substantial equivalence based on these differences is not appropriate under section 905(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act).