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.

U.S. FOOD & DRUG ADMINISTRATION

Memorandum

To: Matthew Holman, Ph.D.
Director
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Digitally signed by Matthew R. Holman -S
Date: 2019.03.01 16:56:33 -05'00'

From: Todd Cecil, Ph.D.
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Through: Colleen Rogers, Ph.D.
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Date: 2019.03.01 14:56:00 -05'00'

Subject: Engineering review of substantial equivalence (SE) Reports for originally regulated products

This memo outlines the Office of Science's (OS) current approach to engineering review of SE Reports.

Role of the Engineering Reviewer in SE Report Reviews

The Engineering reviewer reviews tobacco product manufacturing and design parameters. OS has gained experience in the review of SE Reports for originally regulated products[1] over time. Based on OS's experience, OS's approach to engineering reviews has changed, but the engineering role has not changed. From the inception of the SE program, there has been a need for reviewers to make sound scientific recommendations related to changes in tobacco product design. Engineering reviewers provide the expertise necessary to evaluate changes in design characteristics between the new and predicate tobacco products and the potential effects of these changes. While this evaluation remains important, the approaches previously employed by the engineering staff do not reflect currently available scientific literature and lessons learned. In short, our understanding of originally regulated tobacco products has improved as we have completed more SE reviews, and our current approach reflects changes to incorporate the increased knowledge. The role of an Engineering reviewer in SE review includes identifying potential effects of the changes in design parameters on harmful and potentially harmful constituents (HPHCs) in tobacco products and tobacco smoke, and, where applicable, determining consistency of manufacturing practices to assess the reliability of the test data submitted within the SE Report.

[1] Cigarettes, cigarette tobacco, smokeless, and roll-your-own tobacco products

Background

In its previous approach to engineering review, OS, through Advice/Information Request and Preliminary Finding letters, requested that applicants provide, among other things, target values, range limits, test data, and acceptance criteria for the test data of a set of design parameters. For instance, OS requested test data for each individual design parameter regardless of whether there were differences in the target specifications or if the range limits of the new tobacco product were encompassed by those of the predicate tobacco product. OS is committed to consistency in its approach to review of SE Reports, and, where appropriate, should have identical requirements and outcomes. The previous approach led to some challenges for both OS and industry. These included, among other things, overlapping or duplicative data being submitted by applicants, OS failing to request during review relevant data specific to certain tobacco product manufacturing processes that may be specific to a facility or for a product category design feature, or requests for applicants to provide data on measurements that are not accounted for in their manufacturing process that would not preclude OS from making a determination of substantial equivalence.

Revised Engineering SE Review Process[2]

Beginning in the fall of 2018, based on our current knowledge and understanding of originally regulated tobacco products, engineering reviews have now focused on evaluating the manufacturer's control strategy for tobacco product performance[3] that may affect public health (e.g., delivery of HPHCs). To do this, the Engineering reviewer evaluates three types of information: Manufacturing Data Sheet Specifications (MDSS), critical design parameters as further described below (i.e., product-specific design parameters), and test data. All three types of information are not always necessary for a SE determination; what is required depends on the specific tobacco product under review.

Manufacturing Data Sheet Specifications (MDSS)

The MDSS is a document typically maintained by manufacturers describing all the parameters that are controlled by the manufacturer during the manufacture of their tobacco products. Although the MDSS document describes what is controlled by the manufacturer, it is not necessarily sufficient to demonstrate that the new tobacco product will not differ in other, uncontrolled aspects from the predicate tobacco product in a SE evaluation. This is because the parameters generally listed on the MDSS are related to how a tobacco product is manufactured rather than the how the tobacco product performs in the hands of a user. For example, a manufacturer may not control the percentage moisture in the tobacco used to manufacture a cigarette; instead, they may control the factory floor to a specific temperature and humidity with the knowledge and expectation that the percentage moisture will be maintained within

[2] Note that the SE review process may have up to three rounds of substantive scientific review; therefore, all the information needed may not be available in a particular round of review and deficiencies may be sent to the applicant to request additional information.

[3] Tobacco product performance is a description of the intended delivery of constituents to a user through smoke, aerosol, and saliva. The manufacturer's control strategy is indicated through the evaluation of the design parameters that are actively monitored during production, those that represent quality control checks, and those collected for regulator purposes alone.

their acceptable boundary conditions. This information would be provided in an MDSS instead of the percentage moisture.

Product-Specific Design Parameters (PSDP)

To guide Engineering reviewers and applicants, OS has developed a product-specific list of design parameters (PSDP) now needed for each SE evaluation.[4] The PSDP represents common design parameters that are needed for the evaluation of a tobacco product. Each of these parameters has a known effect upon smoke chemistry and potential effects on user behavior. However, they may not need to be specifically provided if a "substitute" design parameter is provided. There are many potential substitute design parameters that may be appropriate, and each will have to be considered on a case-by-case basis. However, if an applicant does not provide an adequate substitute design parameter on the MDSS, OS will likely include a deficiency asking the applicant to explain either how their provided parameters satisfy the PSDP or ask for a PSDP. Some of the design parameters on the MDSS and the PSDP are likely to be the same; others may be adequately described by alternative parameters on the MDSS. For example, a manufacturer may provide target values for denier per filament (DpF), total denier, filter density, and filter pressure drop in the MDSS. The PSDP for cigarettes indicate that filter efficiency, rather than DpF, total denier, filter density, and filter pressure drop, is required. In this case, the filter efficiency can be calculated from the DpF, total denier, filter density and filter pressure drop and compared to the predicate tobacco product in accordance with the review process described below. Therefore, a request for the filter efficiency ranges and target values would be unnecessary for the evaluation of the tobacco product.

There will be cases in which the design parameters on the MDSS will not directly translate into one of the PSDP. The Engineering reviewer's knowledge of manufacturing processes and the effects of the parameters controlled in the MDSS are necessary to determine if the controls provided by the applicant are sufficient to adequately represent the PSDP. The applicant may need to describe how their controls ensure that PSDP are adequately controlled. For example, MDSS for a new and predicate tobacco product may provide tipping paper specifications that include the number of holes/inch/row, the distance between perforation bands, the perforation band width, the distance from the edge of perforation band to edge of tipping paper, and ventilation hole size, but fail to provide filter ventilation percentage. If a MDSS does not provide filter ventilation percentage, which is a part of the PSDP, it cannot be calculated from other parameters. However, the Engineering reviewer can compare the values of other design parameters to determine whether a change has been made that could cause the new tobacco product to raise different questions of public health (e.g., a change in HPHCs). In this case, OS would not need to request or consider percent ventilation.

[4] Note that since October 2018, the product-specific list of design parameters has been included as an appendix to all Acknowledgement letters (regular SE Reports) and Notification letters (provisional SE Reports). This information is also available on FDA's website.

Physical Test Data

In certain cases, the Engineering reviewer will need to review the test data for indicated design parameters. In a change from previous policy, rather than requiring test data for every design parameter, the Engineering reviewer may examine test data for those design parameters where there is a difference between the target and range limits of the new and predicate tobacco products. In these cases, the test data, test method information, minimum and maximum value, and average test value are each needed in order for the Engineering reviewer to complete their review, as explained below, of the specific design parameter.

First Comparison

The engineering SE review process follows the flowchart as shown in Figure 1 below. The Engineering reviewer first compares the new and predicate tobacco product MDSS. The first comparisons are between the target values and range limits of each design parameter in the MDSS of the new and predicate tobacco products. For each design parameter, if the range limits are the same between the new and predicate tobacco products and the target values are within the range, the Engineering reviewer will not have any concerns with respect to that design parameter. Where the range limits are not the same, but the new tobacco product range limits are entirely encompassed by the predicate tobacco product range limits and the new tobacco product target value is within the predicate tobacco product's range limits, the Engineering reviewer will not have any concerns with respect to that design parameter. All other results of the comparison between the target values and range limits will result in further examination by the Engineering reviewer. Note: the absence of range limits for a parameter in the MDSS is not considered an engineering deficiency if the new and predicate tobacco product target values are identical. This is based on the assumption that deviation from target values is not allowed by the manufacturer (i.e., the range limits are zero). This may be accomplished by the removal, on the production line, of any product that does not conform to the target value. In cases where range limits are absent, any differences in the parameter target value will immediately result in a deferral to the Chemistry reviewer.

Second Comparison

The second comparison is relative to the PSDP and the MDSS. The MDSS describes the parameters actively measured and controlled by the manufacturer; however, the manufacturer does not necessarily control all the parameters that may affect HPHC delivery. The Engineering reviewer evaluates whether the parameters that are controlled correspond to PSDP of the tobacco products. In the cases where the MDSS parameter is sufficient to provide assurance that the PSDP differences are accounted for, then no additional information is needed for the analysis and the results of the first comparison will hold. In cases where the MDSS is not provided or the MDSS does not provide adequate assurance of control of the PSDP, deficiency(ies) requesting target values, range limits, and test data (where necessary) for the tobacco product or products should be included in the review.

There will be cases where the MDSS is not available or the applicant chooses not to provide them. In these cases, the Engineering reviewer compares the PSDP target values and range limits using the review criteria of the first comparison above.

Third Comparison

In cases where the new and predicate tobacco products have different target values and the new tobacco product is not within the range limits of the predicate product, the Engineering reviewer will move on to the third comparison process. In this comparison, the Engineering reviewer will examine the test data for the engineering parameters, along with the methods, average, and minimum and maximum values. If the Engineering reviewer finds that the measured values largely fall within the maximum and minimum limits provided by the applicant, they may determine that the differences in the design parameters do not cause the new tobacco product to raise different questions of public health from an engineering perspective. Otherwise, the Engineering reviewer will evaluate the potential effects that the engineering change might have on the HPHC yields of the tobacco product. However, the evaluation of actual measured HPHC values in the tobacco products will be deferred to the Chemistry reviewer for further evaluation. Where possible, the Engineering reviewer will provide guidance to the Chemistry reviewer pertaining to the potential effects that a design parameter change will have on the tobacco product's HPHC and tar, nicotine, and carbon monoxide (TNCO) delivery. Note that design parameters affect more than the performance of a tobacco product in terms of HPHC yields. Changes to design parameters may also result in changes to user perception, user initiation, or nicotine delivery rate, and, therefore, may be deferred to other appropriate review disciplines.

Figure 1. Decision tree for engineering substantial equivalence review