U.S. FOOD & DRUG ADMINISTRATION

THE SUBSTANTIAL EQUIVALENCE PATHWAY: AN OVERVIEW

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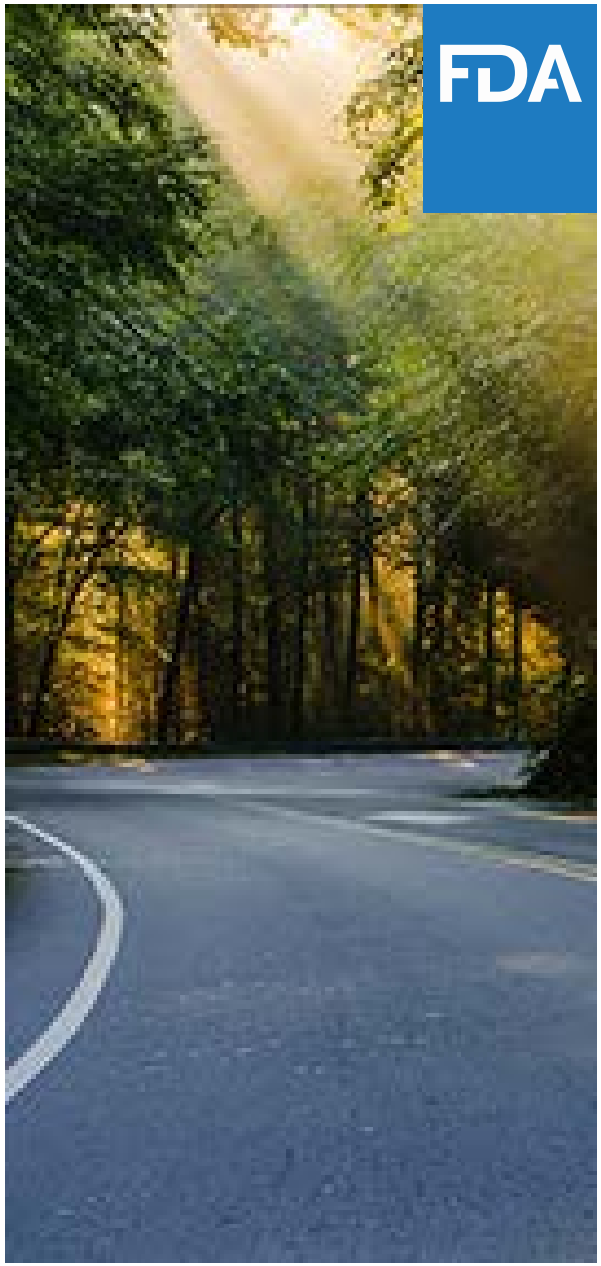
CENTER FOR TOBACCO PRODUCTS

- The Substantial Equivalence (SE) Pathway: Definitions and Statutory Framework
- Description of Review Process from Receipt of Application to Issuance of Decisions
- Description of Statutory Standard and How It Has Been Applied to Date



THE SUBSTANTIAL EQUIVALENCE (SE) PATHWAY: DEFINITIONS AND STATUTORY FRAMEWORK

SUBSTANTIAL EQUIVALENCE (SE) (§ 910(a)(3)) :

The new tobacco product

- has the same characteristics as the predicate tobacco product[2]

OR

- has different characteristics and the information submitted contains information, including clinical data if deemed necessary by FDA, that demonstrates that it is not appropriate to regulate the product under § 910 (premarket application) because the product does not raise different questions of public health.

Characteristics:

The term 'characteristics' means the materials, ingredients, design, composition, heating source, or other features of a tobacco product

Predicate product:

A product that was commercially marketed in the United States (other than in test markets) *as of* February 15, 2007 (Grandfathered) **OR**

A product that was previously found to be substantially equivalent (SE) by FDA

SUBSTANTIAL EQUIVALENCE: STATUTORY FRAMEWORK (§ 910(a)(2)(A)(i))

The manufacturer of a new product is not required to obtain an order under PMTA pathway (910(c)(1)(A)(i)), if

i. the manufacturer has submitted a report under § 905(j); and the Secretary has issued an order that the tobacco product

   I. is substantially equivalent to a tobacco product commercially marketed (other than for test marketing) in the United States as of February 15, 2007; and

   II. is in compliance with the requirements of this Act

SUBSTANTIAL EQUIVALENCE REPORT AND MARKETING STATUS (905(j))

At least 90 days before introduction or delivery for introduction of a new product into interstate commerce for commercial distribution in the United States manufacturers will submit a report

- The report will contain the applicant's basis for determination of substantial equivalence
  - rationale and data to prove the new product is substantially equivalent to the predicate product
  - the new product is in compliance with the FD&C Act

TWO TYPES OF SUBSTANTIAL EQUIVALENCE REPORTS

Provisional Reports:

- New tobacco product introduced into commercial distribution in the United States between 2/15/2007-3/22/2011; AND SE Report submitted by 3/22/2011
- The tobacco product can remain on market unless an order has been issued that the tobacco product is not substantially equivalent to the predicate product

Regular Reports:

- Does not fit criteria for provisional reports
- To be legally marketed in the United States need an order finding new tobacco product is SE to an appropriate predicate product

PRIORITIZATION OF REVIEW OF SE REPORTS

- **Regular Reports:**

- Need an order finding new tobacco product is SE to a predicate product
- The review has been prioritized over provisional reports
- Review starts immediately upon receipt of a report

- **Provisional Reports:**

- All acknowledged provisional SE Reports have received a public health impact (PHI) review
- The reports having the greatest potential to raise different questions of public health were identified and prioritized for review

PUBLIC HEALTH IMPACT (PHI) REVIEW: EXAMPLES OF PRODUCTS THAT MAY HAVE THE GREATEST POTENTIAL TO RAISE DIFFERENT QUESTIONS OF PUBLIC HEALTH

Provisional SE Reports were considered to have the greatest potential to raise different questions of public health if any of the following factors applied:

- Non-conventional new product (e.g., a cigarette contains a bead that can be crushed to release the contents, tobacco stick)
- Inadequate characterization of either the new or predicate product
- Difference in product category between the new and predicate products

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PUBLIC HEALTH IMPACT (PHI) REVIEW:

EXAMPLES OF PRODUCTS THAT MAY HAVE THE GREATEST POTENTIAL TO RAISE DIFFERENT QUESTIONS OF PUBLIC HEALTH (CONT'D):

In comparison to the predicate product:

- Significant increase in total alkaloids or total bases (e.g., quantity of total free nicotine)
- Significant increase in any harmful and potentially harmful constituents (HPHCs) compared to the predicate product
- Significant decrease in acidic ingredients
- Significant difference in tobacco blend (e.g., 50% substitution of burley tobacco)
- Significant design change which was likely to raise questions regarding public health impact (e.g., change in filter ventilation from 50% to 0%)

DESCRIPTION OF REVIEW PROCESS FROM RECEIPT OF APPLICATION TO ISSUANCE OF DECISIONS

CURRENT REVIEW PROCESS

- Phase 1: Administrative/Acceptance
- Phase 2: Notification
- Phase 3: Scientific review and issuance of decision

CURRENT REVIEW PROCESS PHASE 1: ADMINISTRATIVE/ACCEPTANCE

- **Application Received** -- FDA receives and processes the application.
- **Acceptance Review** -- FDA reviews the SE Report to determine if the new tobacco product is under jurisdiction and contains statutory and regulatory mandated items.
  - A new rule, "Refuse To Accept Procedures for Premarket Tobacco Product Submissions" has been issued (Federal Register/Vol. 81, No. 250/Thursday, December 29, 2016, pages 95863 - 95869)
  - The rule became effective from March 21, 2017

REFUSE-TO-ACCEPT PROCEDURES FOR PREMARKET TOBACCO PRODUCT SUBMISSIONS

FDA will refuse to accept a premarket submission that:

(1) Does not pertain to a tobacco product

(2) is not in English (or does not include a complete translation);

(3) is submitted in an electronic format that FDA cannot process, read, review, or archive;

(4) does not include the applicant's contact information;

(5) is from a foreign applicant and does not include the name and contact information of an authorized U.S. agent (authorized to act on behalf of the applicant for the submission);

(6) does not include required form(s);

(7) does not identify the tobacco product;

(8) does not identify the type of submission;

(9) does not include the signature of a responsible official authorized to represent the applicant; or

(10) does not include an environmental assessment or claim of a categorical exclusion, if applicable.

CURRENT REVIEW PROCESS
PHASE 1: ADMINISTRATIVE/ACCEPTANCE

- **Application Received** -- FDA receives and processes the application.
- **Acceptance Review** -- FDA reviews the SE Report to determine if it is under jurisdiction and contains statutory and regulatory mandated items.
- **Issuance of an appropriate letter**
  Acknowledgement Letter -- issues when SE Report meets acceptance criteria
  Refuse to Accept Letter -- issues when the report does not meet acceptance criteria
- **Public Health Impact Review** – FDA completed the public health impact (PHI) review of all acknowledged provisional SE Reports to determine their order in the review queue.

Timeline: FDA has performance goal to finalize acceptance review and issue appropriate letter within 21 days of FDA receipt of SE Report. ((For regular reports of statutorily regulated products)

CURRENT REVIEW PROCESS
PHASE 2: NOTIFICATION

- **Issuance of Notification letter:** For Provisional reports a Notification letter is issued 45 calendar days prior to the start of scientific review.
  - The Acknowledgement letter issued for regular reports inform the applicant that the review started upon receipt of the report.

- **Predicate Determination** -- FDA reviews the predicate tobacco product to validate that it is an eligible predicate.

- **Assignment of Scientific Reviewers** -- reviewers assigned based on contents of the SE Report from the following disciplines:
  - Chemistry, Microbiology, Engineering, Toxicology, Environmental Science, Social Science, Addiction, and Medical

CURRENT REVIEW PROCESS

PHASE 3: SCIENTIFIC REVIEW AND ISSUANCE OF DECISION

- **Scientific Review** -- FDA performs a multidisciplinary scientific review of the SE report to assess the claim for substantial equivalence.

- **Issuance of a Deficiency letter or an Order letter**:
  - **Deficiency letter:** If specific information is needed that would be helpful in making a decision about substantial equivalence, Advice/Information Request (60 days to respond) /or Preliminary Finding letters (30 days to respond) are issued.
  - **Order Letter:** FDA determines whether the new tobacco product is substantially equivalent (SE) or not-substantially equivalent (NSE) to a predicate product, and in compliance with the Act, and issues an appropriate order letter.

Timeline: Review and act on an original SE Report or a resubmission within 90 days of FDA receipt

(For regular reports of statutorily regulated products)

WITHDRAWAL OF AN APPLICATION

- Applicants may withdraw an application at any time.

- If they withdraw the application, FDA issues a letter acknowledging that withdrawal. That ends the process, no matter what phase the application is in.

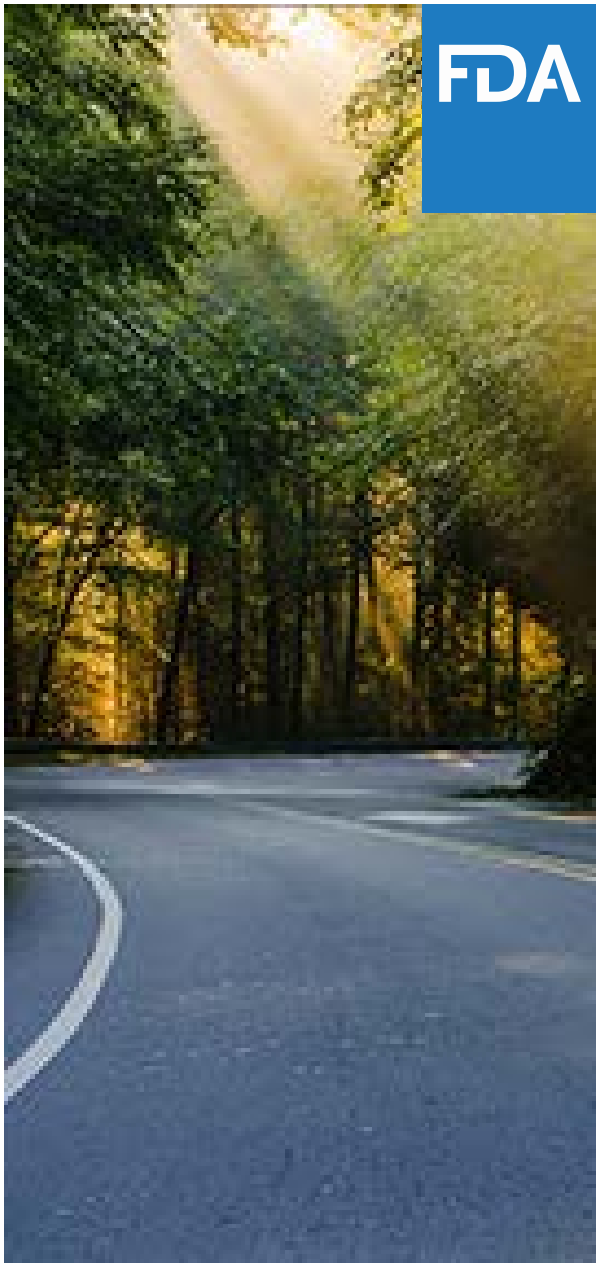
DESCRIPTION OF STATUTORY STANDARD AND HOW IT HAS BEEN APPLIED TO DATE

STATUTORY STANDARD FOR SUBSTANTIAL EQUIVALENCE

Does the new product have the same characteristics as a predicate

or,

if the characteristics are different, do the differences cause the new product to raise different questions of public health?



APPLICATIONS OF PUBLIC HEALTH STANDARD: EXAMPLES FOR A DETERMINATION OF SE

Only Difference in Characteristics between the new and predicate products	Rationale to support a finding of SE
For RYO Paper: 37% decreased length, and 18% decreased width	The smaller dimension is expected to reduce the size of the cigarette when tobacco filler is added to the rolling paper, resulting in lower harmful/potentially harmful constituents (HPHCs) yields.
For RYO Paper: 7% increased guar gum, 8% increased cellulose	Based on calculations the guar gum and cellulose quantities in the new tobacco products would not be expected to generate significant HPHC yields as compared to the predicate product.

APPLICATIONS OF PUBLIC HEALTH STANDARD: EXAMPLES FOR A DETERMINATION OF NSE

Examples	Rationale to support a finding of NSE
Insufficient information for FDA to determine predicate eligibility	FDA cannot issue an SE order if the predicate is not eligible
Inadequate information on design features: ventilation	The changes in design features can alter delivery of harmful/potentially harmful constituents to the user
Significant differences in the tobacco blends between the predicate and new tobacco products.	Tobacco blend differences can result in different levels of harmful and potentially harmful constituents

TAKE HOME POINTS

- SE is an alternative pathway to PMTA
- The new product is compared to the predicate for determination of substantial equivalence
- The regular products cannot be legally marketed without an SE order; the provisional products can remain on the market unless FDA issues an NSE order
- For regular reports of statutorily regulated products, FDA has established performance measures to review and act on an original SE Report or a resubmission within 90 days of FDA receipt.
- It is the applicant's responsibility to provide data and information to FDA to support their claim for substantial equivalence
- In general the TPSAC is not involved in review of the SE Reports