LESSONS LEARNED FROM PMTA REVIEWS

Presented by
Hans Rosenfeldt, Ph.D.
Deputy Director,
Division of Nonclinical Science, CTP, FDA

October 22, 2019

CENTER FOR TOBACCO PRODUCTS

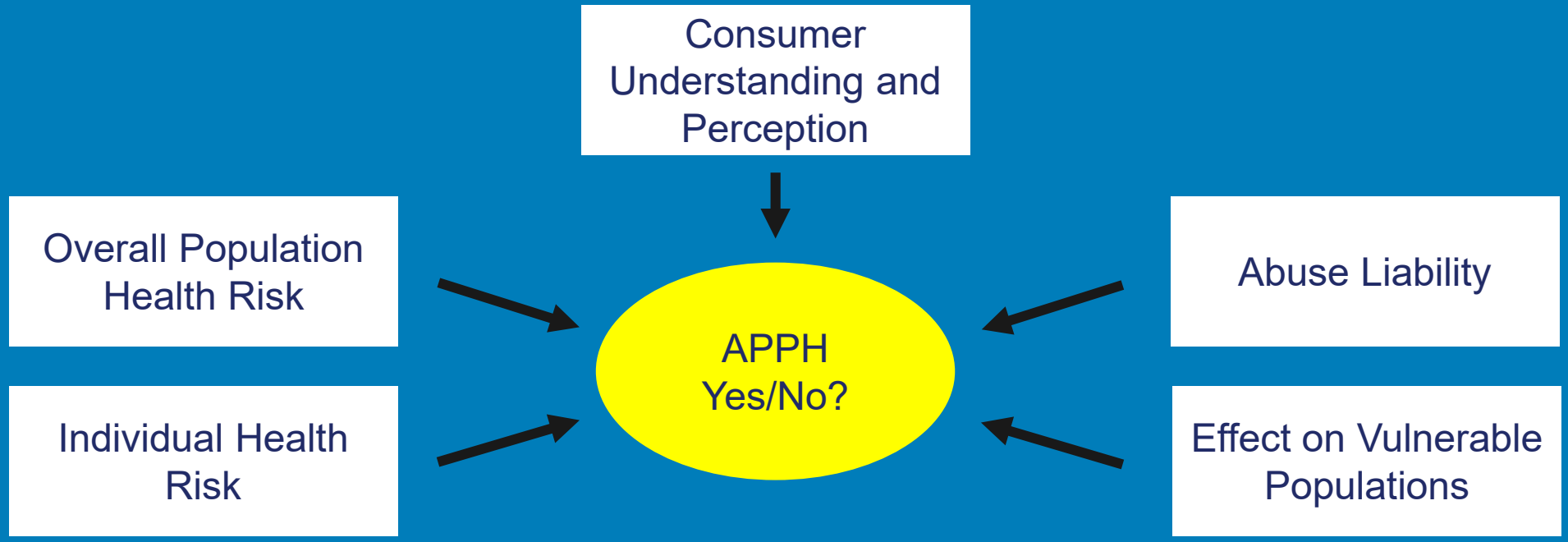
INTRODUCTION

- FDA's goal in product regulation is to reduce the public health risk and individual health risk to the user posed by tobacco products available on the U.S. market.

- For the pre-market tobacco product application (PMTA) pathway, achieving this goal involves the determination of whether the new product described in such a submission is ***appropriate for the protection of the public health*** (APPH) per the FD&C Act as amended by the Tobacco Control Act of 2009.

INTRODUCTION

- As reflected in the draft NPRM on Premarket Tobacco Product Applications and Recordkeeping Requirements, which is currently open for public comment, it is proposed that many different lines of evidence can support the determination whether a new product submitted under the PMTA pathway is appropriate of the protection of the public health.



INTRODUCTION

- Each of these different lines of evidence, may themselves be composed of different kinds of scientific information from published literature or submitted original studies:

Overall Population Health Risk	Individual Health Risk	Consumer Understanding and Perception	Behavioral Pharmacology/ Abuse Liability	Effect on Vulnerable Populations
• Population Models • User behavior studies • Epidemiology studies	• Product Manufacturing and Distribution • Product Ingredients • Product HPHC delivery • Toxicology Studies • Clinical Studies • Biomarker studies (exposure/harm)	• Likelihood of use studies • Comprehension and Perception studies	• Nicotine content • Nicotine and nicotine metabolite pharmacokinetics • Subjective effects	• How new product affects health risks, consumer perception, abuse liability in groups such as: ➢ Pregnant women ➢ Children ➢ Youth and young adults • Affected vulnerable populations depend on the product.

INTRODUCTION

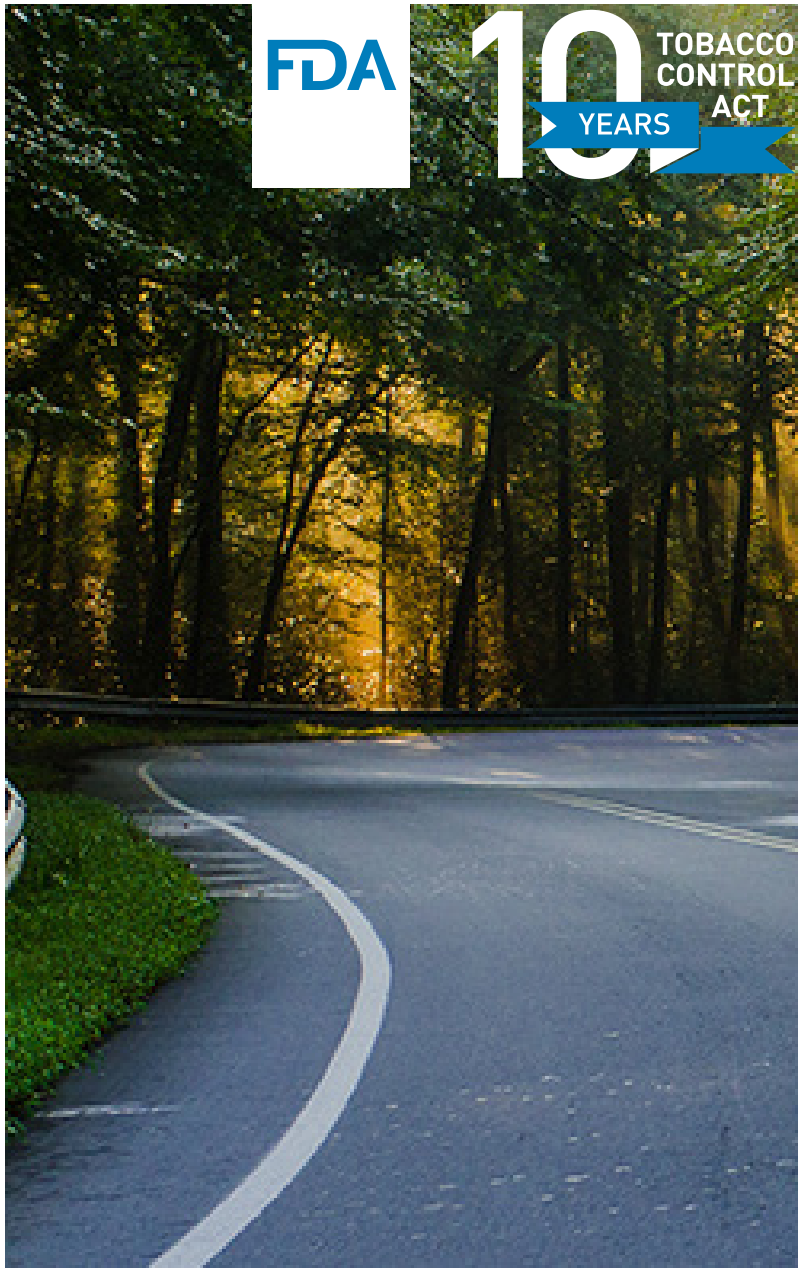
- As reflected in the draft NPRM on Premarket Tobacco Product Applications and Recordkeeping Requirements, which is currently open for public comment, FDA's goal in product regulation is to reduce the public health risk and individual health risk to the user posed by tobacco products available on the U.S. market.
- Thus, evaluation of both the risk to the overall public health and to individual health is a component of FDA's evaluation of PMTAs
- This evaluation includes a health risk comparison between the new product and products that users of the new product would likely use if the new product were not marketed.
- Importantly, all FDA actions under the FD&C Act are also governed by the National Environmental Policy Act (NEPA), which requires that all actions have an associated environmental assessment (EA) or categorical exclusion (CatEx).

INTRODUCTION

- FDA has accumulated some lessons stemming from the review of PMTAs and PMTA meeting request submission materials.
- FDA would like to share these lessons with you in this presentation.
- Most of these issues affect the comparison of the new product in a PMTA to comparator products on the U.S. market and involve review issues important in determining whether marketing of a new product is appropriate for the public health.
- One additional issue that can delay a positive action or cause a negative action is the lack of an adequate EA or a qualified claim of CatEX in the submission. More on this issue later in this presentation.

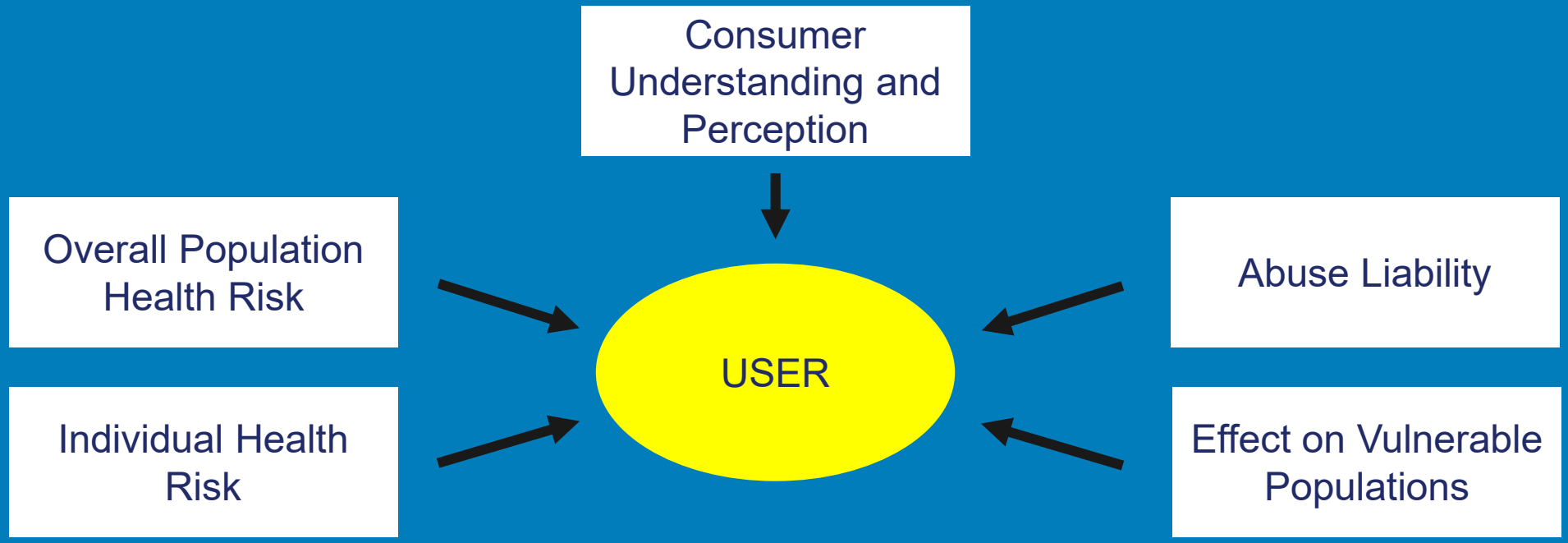
OUTLINE

- **Importance of identifying the user in tobacco product risk comparisons for PMTA**
- Product characterization
- Bridging data
- Product Use Patterns
- Marketing and Advertising
- Environmental Assessments



IMPORTANCE OF THE USER POPULATION

- For each new product, the relative importance of each of these lines of evidence can vary, depending on the **user population**.



IMPORTANCE OF THE USER POPULATION

- As reflected in the draft NPRM on Premarket Tobacco Product Applications and Recordkeeping Requirements, which is currently open for public comment, it is useful to consider the health risks of products that are both within the same category as well as those that are in different categories
- the focus of health risk evaluation of a new product will take into account who the likely user of the new product is.
- Users of the new product are key because the health risk evaluation needs to occur from their point of view:

  If users of a new product in a PMTA are not likely to use combusted cigarettes, for example, then the health risks of combusted cigarettes are less relevant to users of the new product because they are not likely to be exposed to combusted cigarettes.

IMPORTANCE OF THE USER POPULATION

- One central issue in PMTA review is identifying which comparator tobacco products would be used by users of the new product under review if the new product is not authorized to go on the market.
- These tobacco products represent the most relevant comparators for the new product, especially in the context of assessing the health risk posed by the new product:

  The user population can determine the health risk comparisons that are most appropriate for a new product under PMTA.

- Nonusers are also important to the overall APPH evaluation:
  - Users are at greatest risk of tobacco-related disease. This necessitates a focus on users for individual risk determinations.
  - But important issues, such as the potential for initiation, can also affect nonusers.

IMPORTANCE OF THE USER POPULATION

- Tobacco products can be organized along a continuum of risk, as depicted below.
- Currently, the majority of tobacco products sold in the United States cluster along the higher risk end of the spectrum (combusted cigarettes).
- However: Comparing the potential health risk of a new product in a PMTA to combusted cigarettes is not always appropriate.

Continuum of Risk – Not to Scale

IMPORTANCE OF THE USER POPULATION

- Another scenario in which the identity of the user of the new product affects risk comparisons may include:
  - If the likeliest user of the new product is likely to be a user of a tobacco product that is not cigarette – such as an oral tobacco product, the health risk posed by similar non-cigarette products may be compared to the health risk of the new product in the evaluation of the PMTA.
  - In all cases, the effects on non-users are important considerations that need to be assessed.

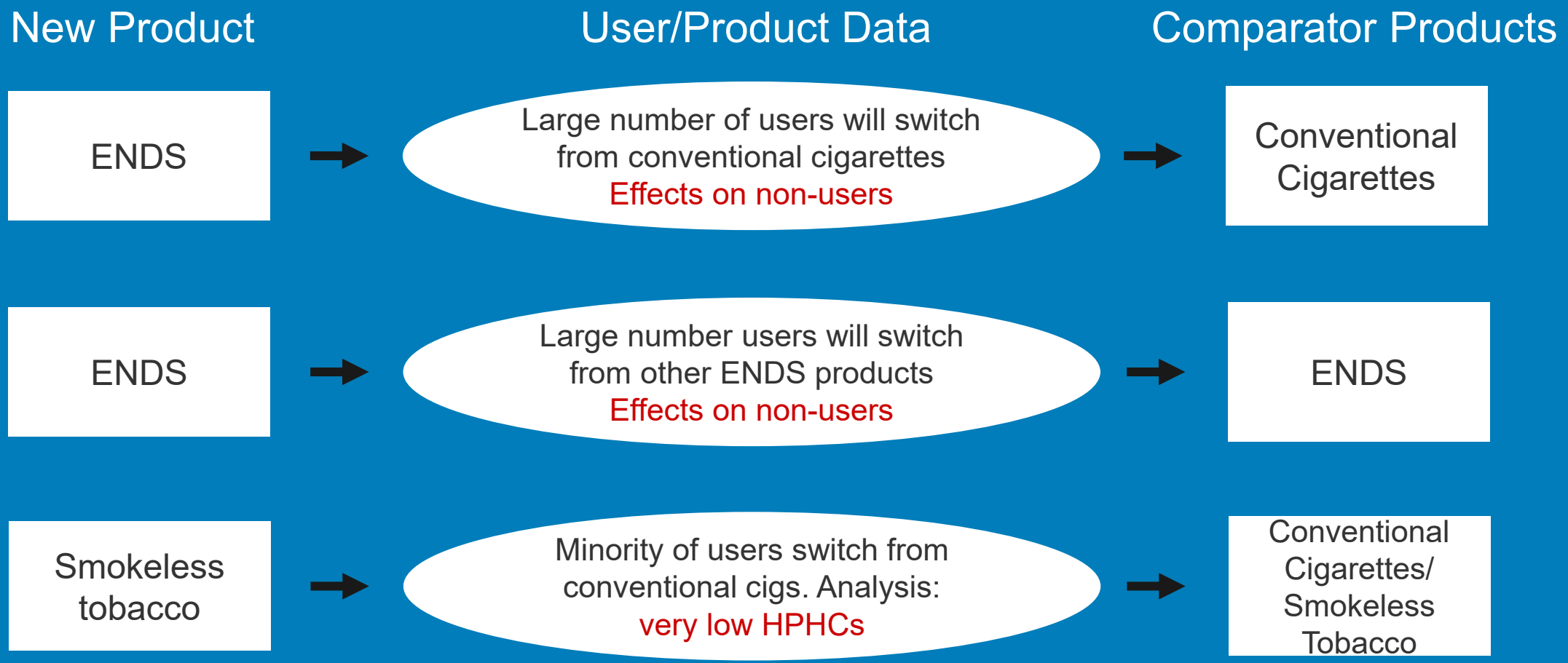
IMPORTANCE OF THE USER POPULATION

- An additional scenario in which the health comparison to more than one product category could be useful:
  - In the case of a new non-cigarette product with very low HPHC deliveries relative to similar products on the U.S. market but a low switch rate from conventional cigarettes, it could be argued that:
    - There is a large drop in individual health risk for the small number of smokers switching to this hypothetical very low HPHC level product.
    - There is, in addition, a drop in health risk for the larger number of users of the same class of tobacco products who would switch to the same hypothetical very low HPHC level product which would result in an overall health benefit to the population.
  - Therefore, a comparison of the new product to conventional cigarettes in addition to similar products on the U.S. market is relevant.
  - Potential effects on non-users are also relevant.

VULNERABLE POPULATIONS

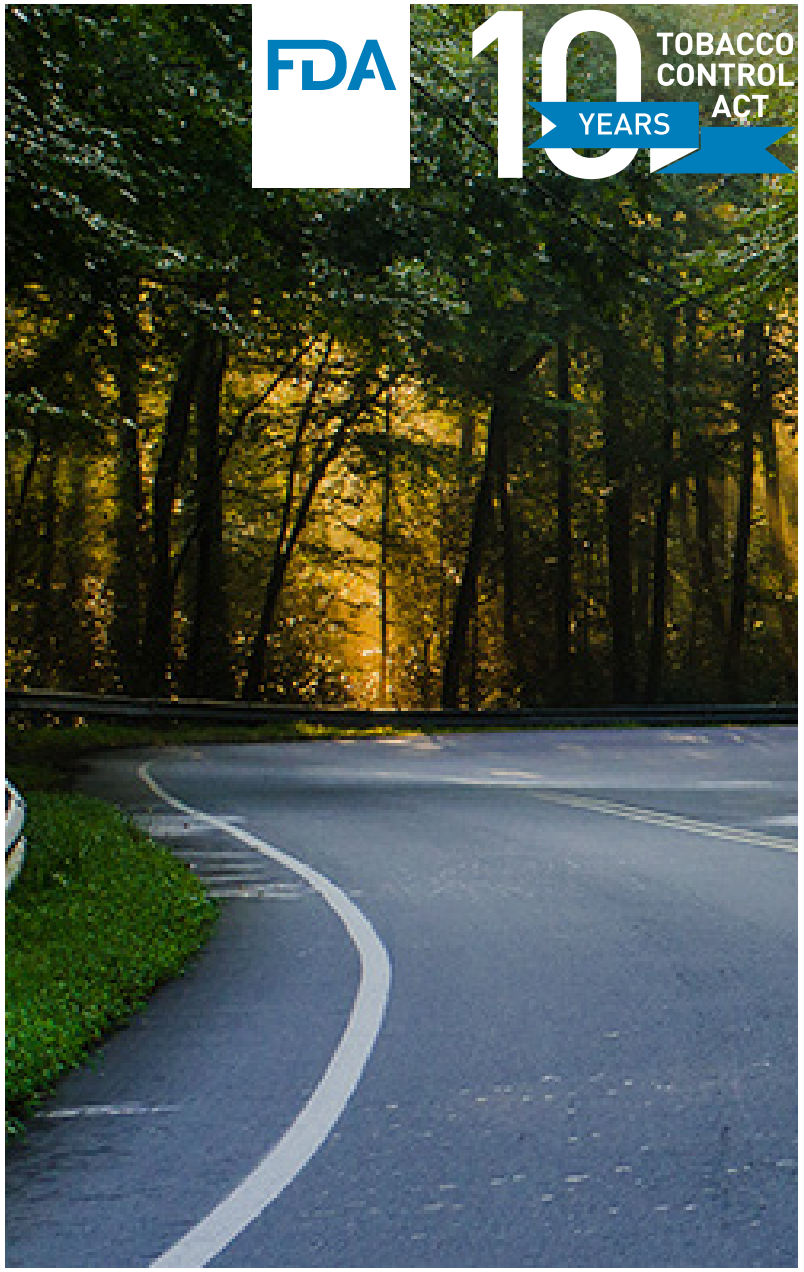
- In some situations, likely users of the new product may be members of vulnerable populations
  - These vulnerable populations could include:
    - Youth
    - Economically or educationally disadvantaged persons
    - Racial/ethnic populations
    - Underserved rural populations
    - People with co-morbid mental health conditions and/or substance use disorder(s)
    - Military/veteran populations
    - Pregnant women or women of reproductive age
    - Sexual and gender minorities
  - These users may:
    - Bear disproportionate burden of tobacco-related disease
    - Have disproportionate use patterns and exposures
- These populations, as appropriate, may be considered in the overall APPH evaluation.
- A disproportionate effect on these populations can affect APPH determination even if they are a minority of likely users.

HYPOTHETICAL EXAMPLES



OUTLINE

- Importance of identifying the user in tobacco product risk comparisons for PMTA.
- **Product characterization**
- Bridging data
- Product Use Patterns
- Marketing and Advertising
- Environmental Assessments



PRODUCT CHARACTERIZATION AND CONTROL

- The following parameters are useful for FDA to define a new product sufficiently under PMTA so that the new product can be compared to relevant products on the U.S. market:
  - Manufacturing processes
  - Manufacturing controls, including controls on HPHCs
  - Complete ingredient information
  - Analytical data, including HPHC data
  - Stability information

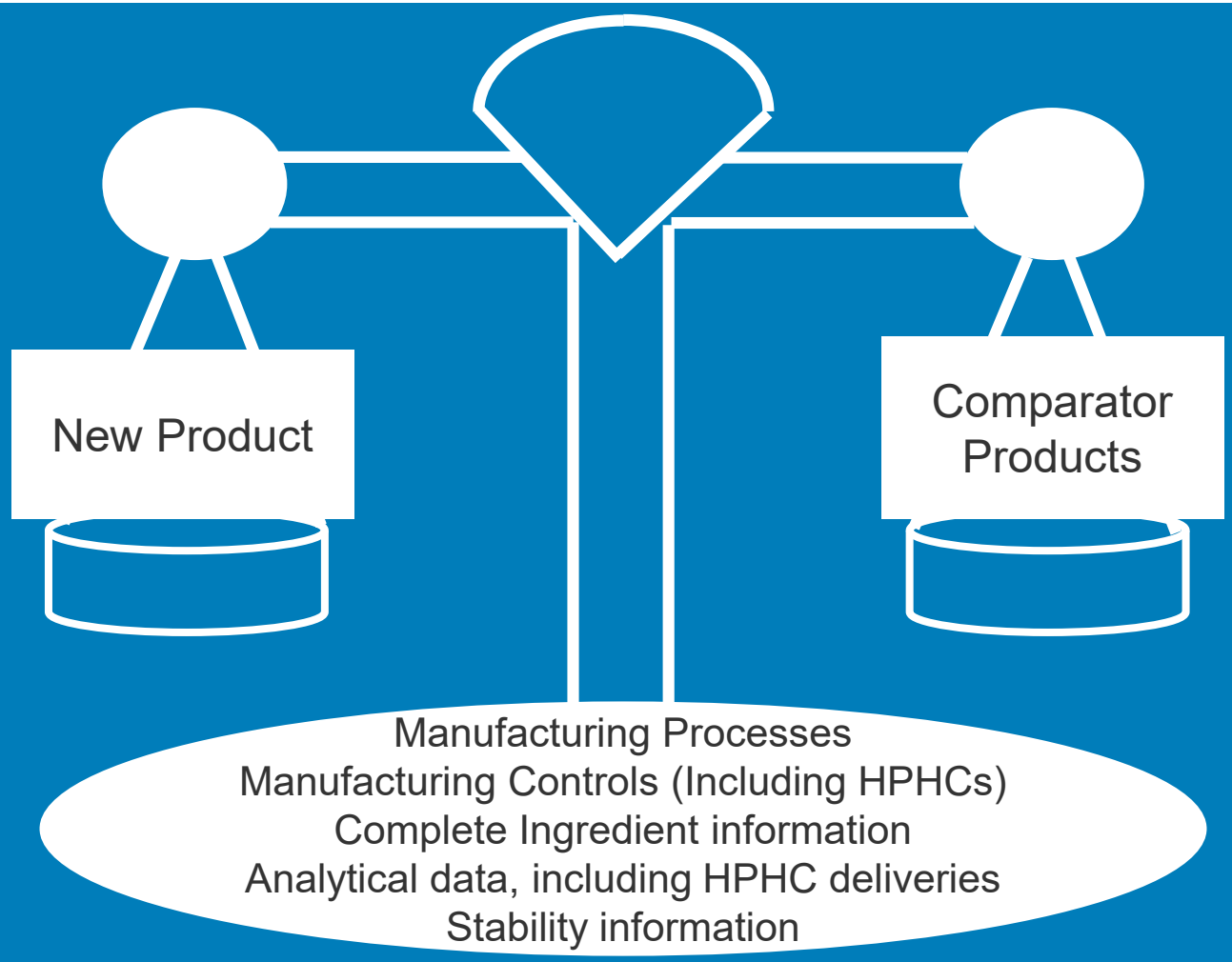
PRODUCT CHARACTERIZATION AND CONTROL

- Product characterization and control is important to the comparison of a new product to comparator products.
- For example, if a new product is manufactured in such a way that HPHC deliveries are NOT consistent over time, it is very difficult to evaluate the health risk of new product relative to comparator products.
- Product characterization also provides important information that the FDA needs to determine that there are no ingredients or degradants of concern in the new product.
- For example, inclusion of toxic additives, stability problems, and the potential presence of toxic leachables are all issues that can affect the health risk evaluation of a new product.

IMPORTANCE OF PRODUCT CHARACTERIZATION

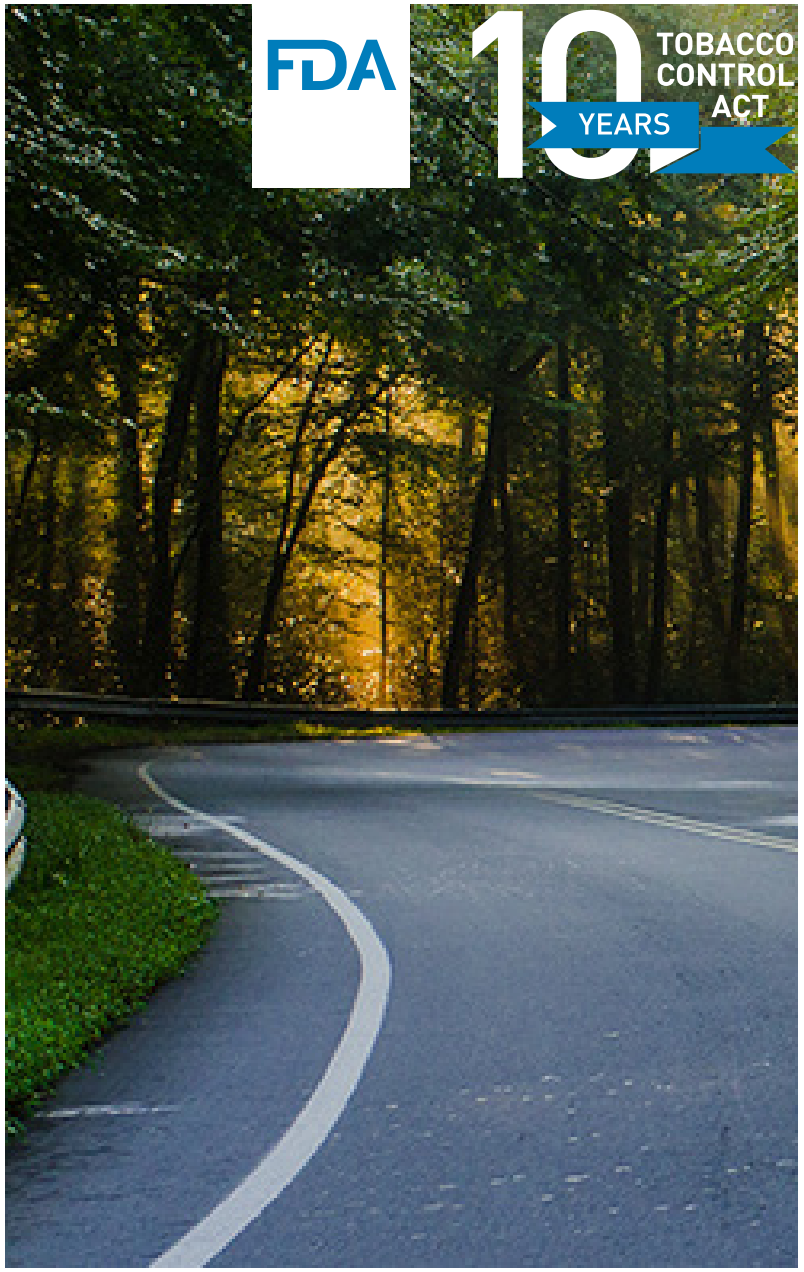
Without good new product characterization, FDA cannot establish whether:

- The product can be manufactured consistently over time
- That the HPHC profile assessed in the PMTA application is relevant to the HPHC profile of the product as it is manufactured in the future.
- That the HPHC comparisons in the PMTA are relevant to the new product as manufactured in the future.
- That the new product will remain stable and not pose further health risk during its shelf life.



OUTLINE

- Importance of identifying the user in tobacco product risk comparisons for PMTA.
- Product characterization
- **Bridging data**
- Product Use Patterns
- Marketing and Advertising
- Environmental Assessments



BRIDGING DATA

- There are two main kinds of data bridging
  - When data generated using a product that is not the new product under review is applied to the evaluation of the new product.
  - When data generated from the study from one population is applied to the evaluation of another population.

BRIDGING DATA – PRODUCT TO PRODUCT

- As reflected in the draft NPRM on Premarket Tobacco Product Applications and Recordkeeping Requirements, which is currently open for public comment, in order for bridge data generated with one product so that it can apply to the evaluation of another product, applicants would need to show that:

  Results from studies of a product that is not the new product under review are applicable to the evaluation of the new product.

- Without this justification the submitted data generated with any other products is of very limited use to the evaluation of a new product listed in a PMTA.

BRIDGING DATA - PRODUCT TO PRODUCT

- Types of studies using test articles that are not the new product under review may include:
  - Studies of product prototypes
  - Studies with products similar characteristics to those of the new product under review
  - Published studies from the scientific literature

- Such studies could include
  - Clinical information, including biomarkers of exposure and harm
  - Nonclinical information, including in silico, in vitro, in vivo, ex vivo toxicology studies
  - Analytical information, including HPHCs delivery data

BRIDGING DATA – PRODUCT TO PRODUCT

- Examples applicable to the draft NPRM on Premarket Tobacco Product Applications and Recordkeeping Requirements, which is currently open for public comment and may change in final rule
  - Toxicology studies of prototype product submitted in support of new product: **strong rationale explaining how results are relevant to new product, HPHC comparison between new product and prototype product, ingredient listing between prototype product and new product provided.***
  - Clinical studies using biomarkers of exposure and biomarkers of harm using a test article different from the new product: **strong rationale explaining how results are relevant to new product, HPHC comparison between new product and prototype product, and ingredient listing between prototype product and new product provided.****
  - Analytical HPHC data using a test article different from the new product: **strong rationale explaining how results are relevant to new product, ingredient listing between prototype product and new product, manufacturing data, and engineering specifications provided.**

*Although not part of bridging, useful for all toxicology tests to include proper experimental controls. For example, for Air liquid interface (ALI) studies of aerosol, useful to include an air-only negative control.
**Although not part of bridging, it is useful to also provide data to support the use of each biomarker as a measure of exposure or as a surrogate clinical endpoint indicating harm.

BRIDGING DATA – PROTOTYPES

- For any protypes used in studies submitted in support of a new product in a PMTA, the following items are useful:
  - That the prototype be clearly named and identified
  - That the prototype be distinguishable from other products referenced in the application, including the new product under review
  - That the prototype be characterized in such a way that submitted studies allow for conclusions about the new product.
  - A rationale indicating why data generated using the prototype can be applied to the evaluation of the new product.

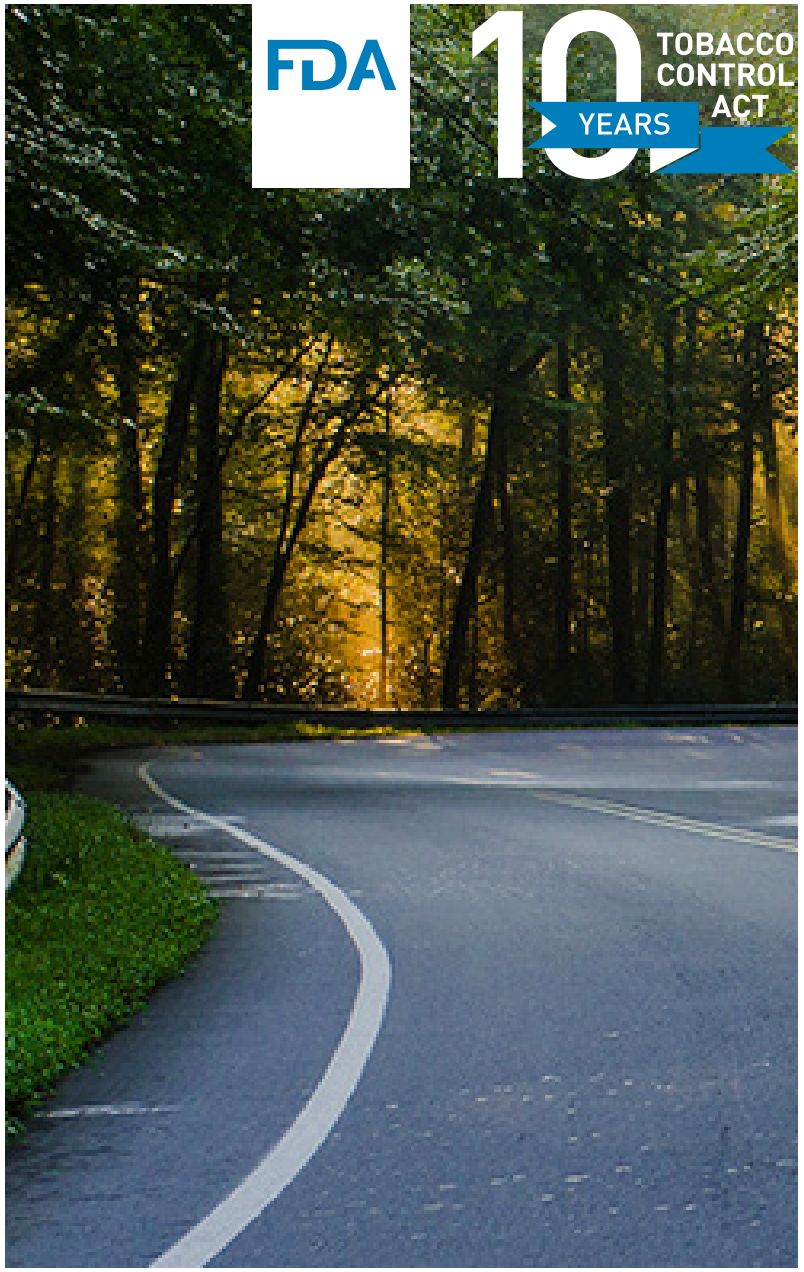
Inclusion of data generated using prototypes without clear identification of the prototypes and without a rationale for why this data applies to the evaluation of the new product is a common problem in PMTA review

BRIDGING DATA – POPULATION TO POPULATION

- Bridging can also occur when data from the results of a study of one population is applied to another population.
  - This kind of bridging can happen with social science, epidemiological, and clinical studies.
  - In such cases, a rationale explaining how data generated from the study of one population can be applied to the population of interest is useful.
  - Important considerations include:
    - Demographic comparison of the two populations
    - Use pattern comparison of the two populations
  - For example, data from a population that has a high prevalence of ENDS use is best compared to another population that also has a high prevalence of ENDS use

OUTLINE

- Importance of identifying the user in tobacco product risk comparisons for PMTA.
- Product characterization
- Bridging data
- **Product Use Patterns**
- Marketing and Advertising
- Environmental Assessments



PRODUCT USE PATTERNS

- A clear description of product use patterns is very useful to establish two very important questions:
  - Who will be exposed to the new product?
  - How much exposure to the new product will occur, and in what context?

- It is generally helpful if the results of product use patterns and likelihood of use studies align with the selection of the comparator products used in the health risk comparison of the new product to the tobacco market.

PRODUCT USE PATTERNS

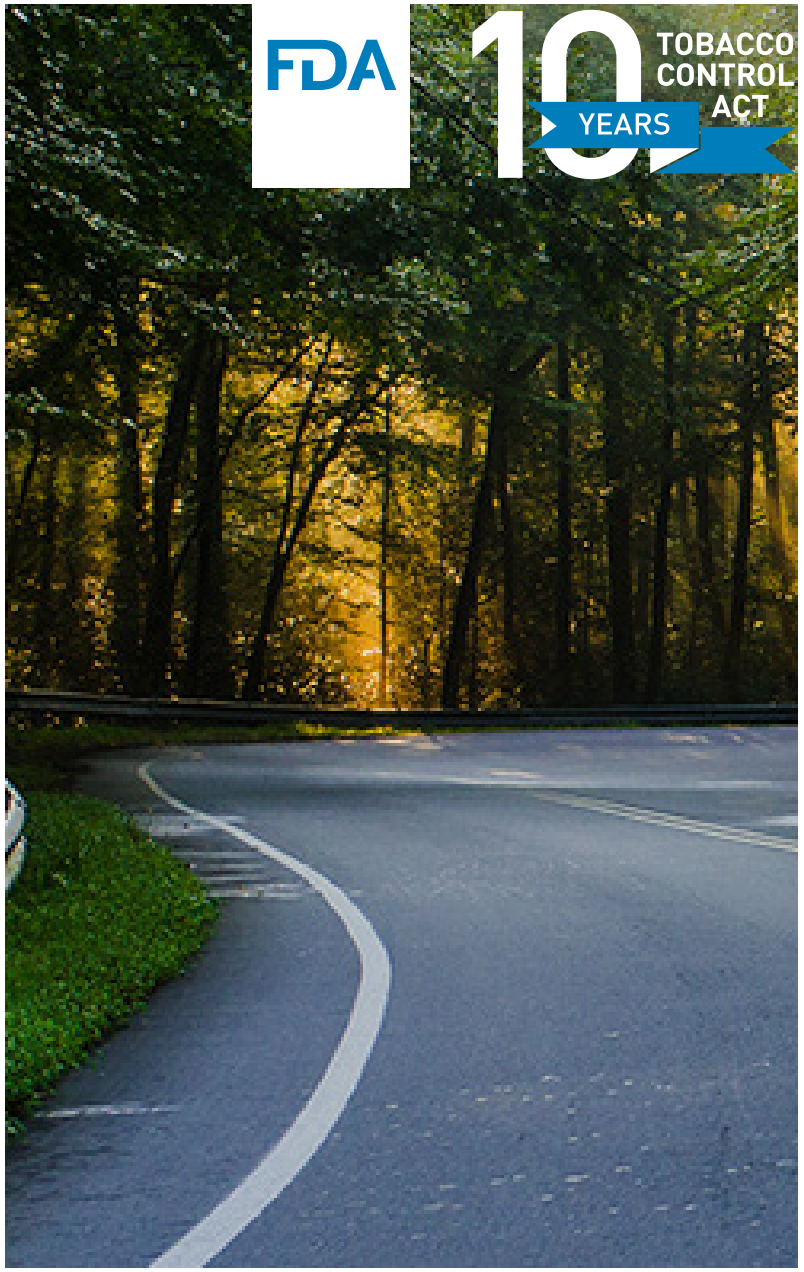
- Product use data can provide important information that can:
  - Determine whether users of one class (for example, cigarettes) are likely to switch to a new product of another class (for example ENDS).
  - Provide information on the youth appeal and the risk of initiation
  - Provide information on the likelihood of dual use.
  - Provide information of human exposure that can be useful for interpretation of toxicology studies
  - Provide data that can be used as inputs for population models that estimate net public health benefit or harm

PRODUCT USE PATTERNS

- As such, product use pattern studies provide very useful information for the overall evaluation of the new product
  - In a useful study endpoints match the effect that they are intended to address
  - For example, if the intent is to measure likelihood of use:
    - a study that measures likelihood of use and provides a direct quantitative measure of likelihood of use is most informative.
    - If a study with an endpoint other than likelihood of use is submitted, provide explanation for why study endpoints were chosen and how they were validated

OUTLINE

- Importance of identifying the user in tobacco product risk comparisons for PMTA.
- Product characterization
- Bridging data
- Product Use Patterns
- **Marketing and Advertising**
- Environmental Assessments

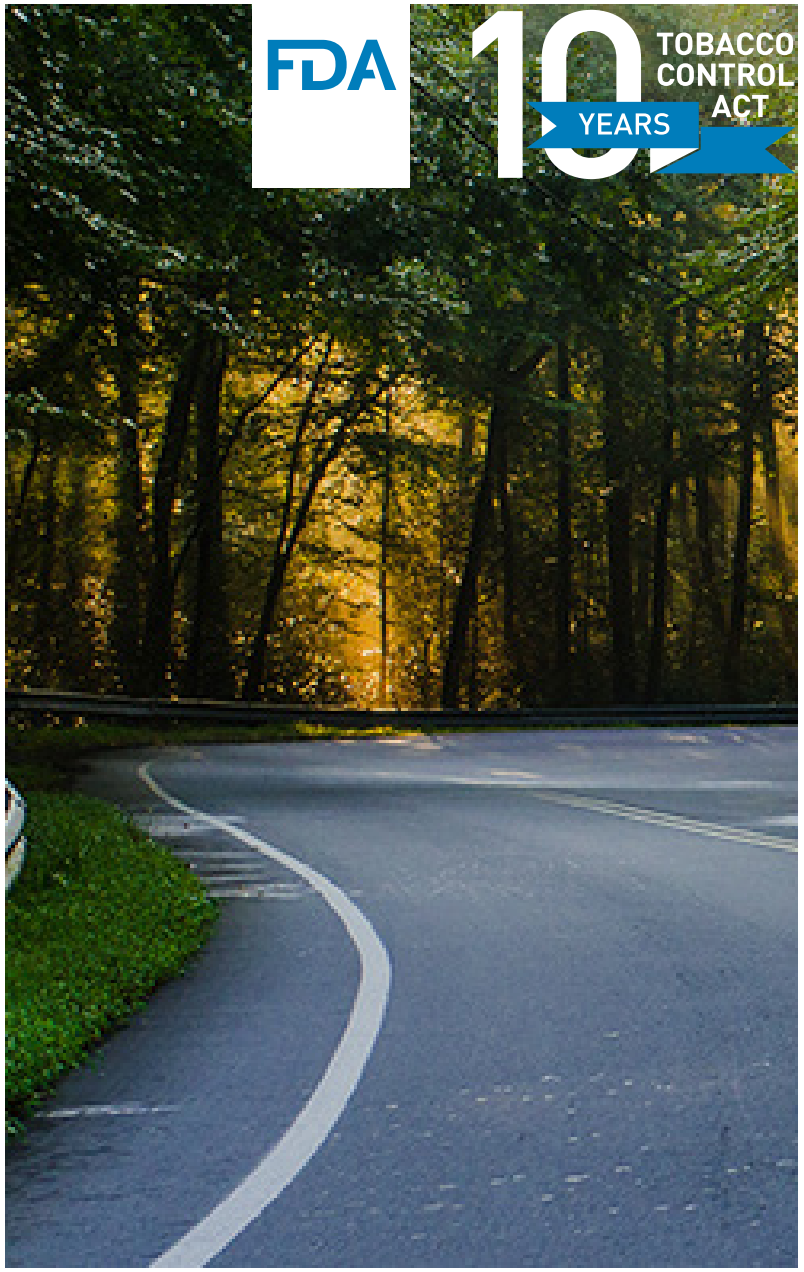


MARKETING AND ADVERTISING

- Submitted advertising should reflect the advertising that will be used if the new products are authorized under PMTA.
- Challenging situations can crop up in the case of parallel PMTA and MRTPA submissions, in which advertising with MRTPA language is submitted with the PMTA.
- For example, the inclusion of modified risk information in advertising materials used in likelihood of use studies that are submitted to both MRTPA and PMTA submissions is problematic for the PMTA.
- PMTA reviewers cannot consider results generated with advertising containing modified risk claims.

OUTLINE

- Importance of identifying the user in tobacco product risk comparisons for PMTA.
- Product characterization
- Bridging data
- Product Use Patterns
- Marketing and Advertising
- **Environmental Assessments**



ENVIRONMENTAL ASSESSMENT

- The need for an environmental assessment (EA) or qualified claim of categorical exclusion (CatEX) for each application is not tied to the APPH determination.

- Instead, an EA is necessary pursuant to the National Environmental Policy Act (NEPA) and 21 CFR 25.15(a), which states “All applications or petitions requesting agency action require the submission of an EA or a claim of categorical exclusion.”

ENVIRONMENTAL ASSESSMENT

- NEPA requires the preparation of an EA for FDA to proceed with a marketing order for a new product under the PMTA pathway.

Lack of an EA is a common reason for PMTA applications not moving forward to scientific review.

ENVIRONMENTAL ASSESSMENT

- What is an EA?
  - An EA is a stand-alone document for the public to understand the government's environmental considerations.
  - Regulations for an EA can be found at 21 CFR 25.40(a)
- Recommended outline of an EA:
  - A cover page
  - A table of contents
  - The body of the EA (more description to come)
  - And any appendices, including confidential appendices that include proprietary marketing information.
- FDA recommends that each EA focus on only one product.

ENVIRONMENTAL ASSESSMENT

- Recommendation for inclusion in the body of an EA:
  - Applicant and manufacturer information
  - Product information
  - The need for the proposed action
  - Alternatives to the proposed action
  - Affected environment
  - Potential environmental impact of the proposed action including manufacturing, use, and disposal of the new product (more description to come)
  - Alternatives, including manufacturing, use, and disposal under alternative scenarios (such as no action)
  - List of preparers
  - List of agencies consulted
  - References

ENVIRONMENTAL ASSESSMENT

- It is recommended that an EA include discussion of the following topics when assessing the environmental impacts of manufacturing, use, and disposal of the product:
  - Air quality
  - Water resources
  - Soil, land use and zoning
  - Biological resources
  - Solid waste and hazardous materials
  - Floodplains
  - Wetlands and coastal zones
  - Regulatory compliance (for example, compliance with Clean Air Act)
  - Socioeconomics and environmental justice
  - Cumulative impacts

ENVIRONMENTAL ASSESSMENT

- Example potential impacts of tobacco products may result from :
  - Manufacturing of the new product
  - Tobacco cultivation
  - Nicotine extraction
  - Synthetic nicotine production
  - Secondhand and thirdhand exposure from use
  - Hazardous waste from disposal of ENDS components and batteries, disposal of waterpipe wastewater, used tobacco, charcoal, cigar butt disposal

ENVIRONMENTAL ASSESSMENT

- FDA would like to emphasize that confidential business information can be included in confidential appendices:
  - According to 21 CFR 25.51(a), confidential business information should be summarized and included in the EA to the extent possible.
  - The EA is a stand-alone and public document and the confidential appendices will remain undisclosed.

CONCLUSION

- As reflected in the draft NPRM on Premarket Tobacco Product Applications and Recordkeeping Requirements, which is currently open for public comment, many different lines of evidence can support whether a new product submitted under the PMTA pathway is appropriate of the protection of the public health, including:
  - An individual health risk comparison
  - An overall population health risk comparison
  - An assessment of consumer understanding and perception
  - An assessment of abuse liability
  - An assessment of effects on vulnerable populations
- It is very important to compare the health risks of a new product to comparator products that are likely to be consumed by users of the new product.

CONCLUSION

- Product characterization and manufacturing controls are very useful to the comparison of a new product to comparator products.
- Health risk evaluations cannot be made without proper characterization of the new product.
- For bridging between products, as reflected in the draft NPRM on Premarket Tobacco Product Applications and Recordkeeping Requirements, which is currently open for public comment and may change in the final rule:
  - Useful information includes a rationale for why results from studies of a product that is not the new product under review are applicable to the evaluation of the new product.

CONCLUSION

- Product use patterns are useful in addressing two questions:
  - Who will be exposed to the new product?
  - How much exposure to the new product will occur, and in what context?

- NEPA requires at least the inclusion of an EA in the PMTA for FDA to proceed with a marketing order for a new product under the PMTA pathway.

- Lack of an EA is a major reason for PMTAs not moving forward to scientific review.