

# Clinical Researcher

## August 2020

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*RETHINKING RISK, RACE, AND OTHER URGENT ISSUES*

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## CLINICAL RESEARCHER—AUGUST 2020 (Volume 34, Issue 7)

### HOME STUDY

#### *RETHINKING RISK, RACE, AND OTHER URGENT ISSUES*

### **Article 1: The Critical Need for Transparency and Disclosure of Participant Diversity in Clinical Trials**

#### LEARNING OBJECTIVE

After reading this article, the participant should be able to summarize the current status and implications of underrepresentation of minority groups in clinical trials, and to describe the significance of the “disparity percentage” concept and how it is determined.

#### DISCLOSURE

Yaritza Peña; Zachary P. Smith; Kenneth A. Getz, MBA: *Nothing to disclose*

**1. Which of the following was passed by the U.S. Congress to address diversity and representation in clinical trials?**

- A. The Food and Drug Administration Amendments Act
- B. The Food and Drug Administration Safety and Innovation Act
- C. The Federal Food, Drug, and Cosmetic Act
- D. The Drug Quality and Security Act

**2. What is one purpose of the FDA’s Drug Trial Snapshots?**

- A. To present details on the disease burdens faced by ethnic populations for which approved New Molecular Entities have been tailored.
- B. To present justifications for follow-up trials of approved New Molecular Entities to be conducted in additional demographic subgroups.
- C. To present arguments for and against broadening the inclusion criteria for ethnic minority participants in trials of New Molecular Entities.
- D. To present observed differences in safety and efficacy by demographic subgroup in trials of approved New Molecular Entities.

**3. The Tufts CSDD survey described in the article had which of the following objectives?**

1. Solicit opinions on likelihood of trial participation from demographic subgroups.
2. Gather data on participant demographic subgroup disparities in trials.
3. Target sites with funding for outreach efforts to new demographic subgroups.
4. Assess participant demographic subgroup data from sponsor companies.

- A. 1 and 2 only
- B. 1 and 3 only
- C. 2 and 4 only
- D. 3 and 4 only

**4. Which of the following is a term for a metric designed to characterize participant demographic subgroup underrepresentation?**

- A. Disparity percentage
- B. Minority index
- C. Diversity quotient
- D. Ethnicity fraction

**5. How many drug approvals examined by Tufts CSDD lacked participant ethnicity data for the trials conducted?**

- A. 10%
- B. 30%
- C. 50%
- D. 70%

**6. Under-representation in pivotal trials was found to be worst for which minority population?**

- A. Native American
- B. Hispanic or LatinX
- C. Asian
- D. Black or of African descent

**7. The authors caution that treating minority populations as homogeneous could have negative results in which of the following patient-related areas?**

- A. Stereotypes and biases
- B. Billing and finances
- C. Compliance and consent
- D. Randomization and blinding

**8. For proper representation to have occurred, how many more Black/African American participants do the authors say should have been enrolled in trials in the time period observed?**

- A. Twice as many
- B. Three times as many
- C. Four times as many
- D. Five times as many

**9. Among the Asian subgroup, which therapeutic area had the highest average disparity percentage per drug?**

- A. Pulmonary/respiratory diseases
- B. Rheumatology
- C. Gastroenterology
- D. Neurology

**10. Which of the following is noted as a limitation of the study by the authors?**

- A. No assessment of device studies compared to drug studies was conducted.
- B. No assessment of non-U.S. citizens participating in the studies was conducted.
- C. No assessment of financial impacts of study participation on patients was conducted.
- D. No assessment of non-FDA-approved drug development programs was conducted.

## **Article 2: A Review of the FDA Process, Implementation, and Future Directions for the Approval of Electronic Nicotine Delivery Systems (ENDS)**

### LEARNING OBJECTIVE

After reading this article, the participant should be able to explain the history and purpose of the Tobacco Control Act, its functions in relation to ENDS products, and the current Pre-Market Tobacco Application approval process.

### DISCLOSURE

Mario Esquivel, MS, ACRP-CP: *Nothing to disclose*

**11. Which of the following actions was part of the Tobacco Control Act?**

- A. Mandated trials for proposed new tobacco products.
- B. Restrictions on tobacco advertising to children.
- C. Establishment of health benefit goals for smoking.
- D. Funding of reparations for second-hand smoking effects.

**12. What was the FDA's first legislative attempt to reign in tobacco products?**

- A. The Food, Drug, and Cosmetics Act
- B. The Tobacco Control Act
- C. The FDA Rule
- D. FDA v. Brown and Williamson Tobacco

**13. What was the range of FDA’s authority over cigarettes under the Tobacco Control Act?**

- A. All related marketed and proposed products.
- B. Only newly proposed or updated products.
- C. Proposed products undergoing clinical trials.
- D. Only products already in the market.

**14. What guidance declared all tobacco and ENDS products to be under FDA’s purview?**

- A. The Tobacco Control Act
- B. The FDA Rule
- C. The Deeming Rule
- D. The Pre-Market Tobacco Application

**15. Review and approval processes for ENDS devices are similar to what other processes?**

- A. Rules for FDA medical device regulatory pathways.
- B. Guidance on conducting trials of drug delivery patches.
- C. Phase IV post-marketing surveillance studies.
- D. Best practices for using placebos in randomized trials.

**16. A PMTA should provide data demonstrating which of the following about an ENDS product?**

- 1. Appropriate controls and manufacturing processes were used to make it.
- 2. The overall risks or benefits of the product.
- 3. How likely tobacco users or non-users are to be users due to the new product.
- 4. Clinical trials for the product are unnecessary.

- A. 1, 2, and 3 only
- B. 1, 2, and 4 only
- C. 1, 3, and 4 only
- D. 2, 3, and 4 only

**17. What kind of ENDS products does the Substantial Equivalence Exemption pathway to approval under the Tobacco Control Act focus on?**

- A. Those that provide medical benefits similar to anti-addiction drugs.
- B. Those that have already been approved but must be modified.
- C. Those that may be found “substantially equivalent” to a predicate product.
- D. Those that are designed to only be used once and then disposed of.

**18. When did the first PMTA approvals for ENDS products happen, and for how many?**

- A. Two in 2017
- B. Three in 2018
- C. Four in 2019
- D. Five in 2020

**19. The author notes which of the following as being an effect of the Tobacco Control Act?**

- A. More smaller companies are introducing safer products to the market.
- B. Public demands for clinical trials of tobacco products have risen dramatically.
- C. New ENDS products are practically guaranteed to receive FDA approval.
- D. Larger companies have a competitive advantage over smaller companies.

**20. What market shift does the author describe as currently being under way?**

- A. From traditional cigarettes to ENDS products.
- B. From ENDS products to disposable cigarettes.
- C. From disposable cigarettes to nicotine patches.
- D. From traditional cigarettes to chewable products.

PEER REVIEWED

## **The Critical Need for Transparency and Disclosure of Participant Diversity in Clinical Trials**

Yaritza Peña; Zachary P. Smith; Kenneth A. Getz, MBA



It is well known that the underrepresentation of minority groups in clinical trials decreases the generalizability of clinical trial findings by disguising the potential effects of variation in the pathobiology of disease and race-related differences in drug responses. As a result, several regulatory policy initiatives have focused on developing clinical trial enrollment practices that improve the inclusion of diverse patient subpopulations.

The U.S. Food and Drug Administration (FDA) first released guidance about the importance of studying the effects of products in elderly patients in the 1980s.<sup>{1}</sup> A decade later, the agency issued a “Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs” and established the Office of Women’s Health. Despite the progress made as a result of these guidance documents, underrepresentation of racial and ethnic minorities in clinical trials remained highly prevalent.

In 2012, the U.S Congress passed the Food and Drug Administration Safety and Innovation Act (FDASIA) to address ongoing concerns over the lack of diversity and representation in clinical trials. Section 907 of the Act calls for the FDA to improve the inclusion and transparency of clinical trial data representing demographic subgroups.<sup>{1,2}</sup> In 2013, a cross-agency task force involving representatives from the Office of the Commissioner, the Center for Biologics Evaluation and Research (CBER), the Center for Drug Evaluation and Research (CDER), and the Center for Devices and Radiological Health (CDRH) found that the FDA’s statutes,

regulations, and policies generally provided product sponsors a solid framework for disclosing data on the inclusion of demographic subgroups in their applications. { 1 }

In 2014, the FDA responded with a new annual publication called “Drug Trial Snapshots.” This publication routinely discloses the extent to which Section 907 of the FDASIA is applied in biomedical research; the print and online versions present the demographic distribution of participants in clinical trials of approved New Molecular Entities (NMEs) for that given year as well as any observed differences in safety and efficacy by demographic subgroup.

Conclusions regarding these differences, however, cannot always be made from the Snapshot reports alone. The data they provide are limited to individual years, thwarting researchers from evaluating trends in participant subgroup demographics.

Aside from FDA recommendations, there are no regulations currently in place that require industry sponsors to include women and minorities in their trials and no programs that provide insight into missing data. {3,4} Perhaps most importantly, current guidance documents do not disclose the information necessary to assess disparities in demographic diversity given individual disease prevalence rates.

### **What We Need Versus What We Have**

More comprehensive data on participant demographic subgroups may aid clinical research professionals in identifying opportunities to improve diversity in their research sites.

Specifically, it can help to identify the areas of greatest need, including where demographic subgroup disparities are the greatest, both overall and within specific therapeutic areas or disease conditions.

The information can also be used to assess how participant diversity has changed over time. The availability of results may promote innovations in clinical trial design and avoid duplication of unsuccessful diversity programs or policies, thereby avoiding unnecessary risks to research participants.



To address the need for more comprehensive data and to establish a global baseline measure, in 2019, the Tufts Center for the Study of Drug Development (CSDD)—supported by a research grant from Merck Sharp & Dohme Corp.—conducted a study to address the following objectives:

- Assess the availability and disclosure of participant demographic subgroup data provided by pharmaceutical and biotechnology companies.
- Gather data to inform a baseline assessment of the extent of participant demographic subgroup disparities in the clinical trials of new drug approvals.
- Establish and convey an approach that the FDA, and other stakeholders alike, can apply to improve the value of the Drug Trial Snapshots program and other diversity initiatives.

Since supplemental trials are not required to be reported, this article focuses on disparity in pivotal trial data.

## **Methods**

Tufts CSDD compiled participant demographic subgroup data (i.e., sex, race, ethnicity, age) from pivotal trials supporting all new drugs and biologics approved by the FDA between 2007 and 2017 (n=341). Most of the data were drawn from the FDA website. Tufts CSDD referred to publicly available sources, including ClinicalTrials.gov, medical reviews, and product labeling. Prevalence and incidence data were collected from published sources, including government websites, national health organizations, and peer-reviewed literature.

Tufts CSDD created a summary metric, called the “disparity percentage,” to characterize participant demographic subgroup underrepresentation. This metric is defined as the difference between total actual number of participants by subgroup and the expected level of subgroup representation, divided by the expected level of subgroup participation.

Disease prevalence rates were found in the peer-reviewed literature and public sources for 57% of all approvals. For the remaining 43%, U.S. census data were used as a proxy for the distribution of participant demographic subgroups, as it was assumed that prevalence was distributed proportionately among the population.

Data on 757 pivotal clinical trials and 592,168 study participants were analyzed. An example of the disparity percentage is shown in Figure 1:

**Figure 1: Calculating a Disparity Percentage**

Disease Condition for Approved Drug:	Peripheral T-Cell Lymphoma
Total Clinical Trial Participants:	788
“Actual” Distribution of Participants Who are Black or of African Descent:	3.7% (29 participants)
Expected or “Predicted” Distribution of Participants Who are Black or of African Descent:	13.5% (106 participants)
<b>Disparity Percentage</b>	<b>-72.6%</b>

## Results/Discussion

### *Data Completeness*

While government guidelines mandate that federally funded clinical research to disclose participant demographic data, race/ethnicity data remain incomplete and underreported. Nearly 20% of all drug and biologic approvals between 2007 and 2017 were missing data on participant race for all referenced pivotal trials. More surprisingly, 50% of drug approvals did not include participant ethnicity data on any of their trials (see Table 1).

The level of drug approval data completeness showed notable increases in participant representation by sex and age at 96.2% and 91.8%, respectively. The availability of demographic data for pivotal clinical trials showed a similar pattern, with higher completion rates for participant sex (89.7%), age (83.2%), and race (72.8%) and a considerably lower level of availability rate for study participant ethnicity (36.7%).

The availability of participant demographic subgroup data for all 757 pivotal clinical trials approved in the 10-year period was substantially low; only 36.7% had data available on participant ethnicity and 72.8% of trials had data on participant race. The dearth of available

ethnicity data represents both the need to enroll more minorities in studies and the need to be more intentional in referencing health disparate populations.

**Table 1: Data Transparency in NDAs and BLAs, 2007 to 2017**

	<b>NDAs and BLAs with Data Available on Participants (n=341)</b>	<b>% of Total</b>	<b>Pivotal Trials with Data Available on Participants (n=757)</b>	<b>% of Total</b>
<b>Sex</b>	328	96.2%	679	89.7%
<b>Race</b>	282	82.7%	551	72.8%
<b>Ethnicity</b>	171	50.1%	278	36.7%
<b>Age</b>	313	91.8%	630	83.2%

*Note: Drug data collected from the FDA website. Pivotal trial data collected from the FDA drug information portal for medical reviews and printed labeling for each approved drug.*

#### *Participant Demographic Subgroup Representation*

The highest overall levels of underrepresentation were observed among participants of Black or of African descent, with nearly 47,000 fewer participants than expected (see Table 2). “Other” participants (e.g., Native American, Native Alaskan, Native Hawai’ian, or Pacific Islander) and Hispanic or LatinX participants were also under-represented, with 11,641 and 4,669 fewer participants than expected, respectively. Roughly 20,000 fewer women were enrolled in pivotal clinical trials than expected levels. Asian participants were over enrolled by more than 23,000 participants in pivotal trials, a disparity of +148.9%.

Overrepresentation among Asian participants may be due, in part, to market access requirements in key geographies including Japan and China.<sup>{5}</sup> However, country-specific variation in the characterization of demographic subgroups may also be a contributing factor. Some studies counted participants of Indian descent as Asian while others did not.

Treating minority populations as homogeneous assumes cultural beliefs and experiences are the same, which could potentially influence racial/ethnic stereotypes about patients and implicit

biases in research settings.{6} Understanding cultural differences within subpopulations could emend the cycle of participant distrust in clinical research.

Moreover, inconsistent implementation of racial/ethnic classifications negatively impacts participant disparity percentages. Any significant differences found between groups differentially affects the generalizability of clinical research. Disaggregated analyses may increase our ability to understand exposures and health outcomes across subgroups.{7}

**Table 2: Subgroup Disparities for Pivotal Trials (n=757)**

	Sex		Race and Ethnicity				
	Female	Male	White	Black	Asian	Hispanic /LatinX	Other
<b>Total participants</b>	252,586	309,844	346,884	24,612	39,244	32,877	13,612
<b>Distribution of total participants</b>	44.9%	55.1%	75.9%	5.4%	8.6%	7.2%	3.0%
<b>Expected level of participation*</b>	272,616	288,137	305,443	71,226	15,764	37,546	25,253
<b>Expected distribution</b>	48.6%	51.4%	67.1%	15.6%	3.5%	8.2%	5.5%
<b>Difference</b>	-20,030	+21,707	+41,441	-46,614	+23,480	-4,669	-11,641
<b>Disparity percentage</b>	-7.3%	+7.5%	+13.6	-65.4%	+148.9%	-12.4%	-46.1%

*\*Based on U.S census and disease prevalence.*

Wide variation was observed in the disparity percentages for participant demographic subgroups by individual disease condition. Pulmonary/respiratory disease, neurology, and rheumatology require the most attention and remediation, with racial and ethnic disparities observed for more than 80% of the total approvals for these indications (see Table 3). While these diseases disproportionately affect non-white individuals, pivotal trials in these areas had the highest under-representation of Black/African Americans, Hispanic/LatinX and “Other” subgroups.

Black/African American representation in pivotal trials conducted during 2007 through 2017 was considerably low. Based on the analysis of the data available, three times as many Black/African American participants should have been enrolled in clinical trials during the period observed to be adequately represented by disease prevalence rates or by population census figures. Similarly, the Hispanic/LatinX community was highly underrepresented in pivotal trials of investigational oncology treatments. Gastroenterology and rheumatology were the two top therapeutic areas with high levels of Asian participant under-representation.

**Table 3: Top Therapeutic Areas with Participant Demographic Disparities**

<b>Subgroup</b>	<b>Therapeutic Area</b>	<b>Approved Drugs which Underrepresent Demographic (&gt;20%)</b>	<b>Average Disparity Percentage per Drug</b>
Black/African American	Pulmonary/respiratory diseases	100%	-80%
	Rheumatology	100%	-80%
	Neurology	88%	-70%
Asian	Gastroenterology	100%	-86%
	Rheumatology	83%	-46%
Hispanic/LatinX	Oncology	93%	-63%
	Neurology	85%	-54%
	Pulmonary/respiratory diseases	80%	-51%
Other Racial Identities	Neurology	89%	-72%
	Pulmonary/respiratory diseases	86%	-72%
	Immunology	100%	-71%

## **Conclusion**

Findings from the Tufts CSDD study highlight not only the need to improve transparency and reporting of clinical trial participant demographic data, but also the high level of participant subgroup under-representation in FDA-regulated pivotal trials during the past 11 years.

Developing trust between study participants and clinical research professionals begins with improvements in transparency and disclosure. The results of this study indicate efforts to improve participant diversity have not been broadly successful and more needs to be done.

This study has its limitations. The analysis is based on publicly available data. As a result, the findings may underestimate participant subgroup diversity levels. It is likely that sponsor companies collected but did not report participant demographics for some of their trials; further emphasizing the need for disclosure and reporting in the industry.

The results do not include an assessment of drug development programs that failed to receive FDA approval. Additionally, Tufts CSDD relied on U.S. census data to determine the expected or predicted level of population demographic representation when disease-specific prevalence rates were unknown. Future research will look to apply country-specific population census data and other study exclusion criteria to improve the accuracy of diversity assessment.

Low levels of trust, poor access, study participation burden, low education, and lack of clinical trial awareness are among the many barriers that contribute to minority under-representation in clinical research. Poor disclosure and transparency have contributed to public distrust.{8} Improvements in data reporting and completeness on participant demographic diversity will not only go far in improving public trust, they will also play a key role in guiding the clinical research enterprise in addressing the under-representation of participants by race and ethnicity.{9}

## **Authors' Notes**

*Data collection began in 2018 and continued into 2019. While more current data are available now, these were not available at the time our data collection was completed and were out-of-*

scope for the project being conducted. Tufts plans to periodically update the dataset with more current data. In calculating the impact of FDASIA, we see little evidence of change over time for the years leading up to and after 2012, but in time an examination of this topic may make up its own paper.

Kenneth A. Getz reports an educational grant from the Investigator-Initiated Studies Program of Merck Sharp & Dohme Corp. during the conduct of the study.

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PEER REVIEWED

## **A Review of the FDA Process, Implementation, and Future Directions for the Approval of Electronic Nicotine Delivery Systems (ENDS)**

Mario Esquivel, MS, ACRP-CP



*Tobacco use in the United States amongst adults has consistently been the leading cause of preventable death.<sup>{1}</sup> Smoking adoption by men and women had steadily increased between 1900 and 1960, but has been on the decline ever since.<sup>{2}</sup> Tobacco control measures had been put in place to curb the use; however, a national policy regarding the oversight of tobacco products was not passed until 2009, with the arrival of the Family Smoking Prevention and Tobacco Control Act (Tobacco Control Act). This legislation granted the U.S. Food and Drug Administration (FDA) the ability to regulate tobacco products. In this paper, I will examine the current application process for tobacco products—more specifically, electronic nicotine delivery systems (ENDS).*

### **Background**

Among other things, the Tobacco Control Act imposed new warning label requirements and label standards on tobacco packaging, banned flavored cigarettes, reigned in tobacco advertising to children, and initiated a process for tobacco products to receive approval from the FDA prior to marketing. The impact of the pre-market review process on tobacco products cannot be understated—tobacco products were previously regulated through Congressional regulations that dealt with the sale to minors and distribution licensing of products rather than public health.

Before passage of the Act, Congress had sole authority in the regulation of tobacco products.{3} This was a result of the overturning of the FDA Rule by the Supreme Court in 2000. The FDA Rule was, legislatively, the agency's first attempt to reign in tobacco products and demonstrate that they were under its authority. It was a unilateral decision by the FDA, in order to reduce tobacco use in minors.{4}

The Supreme Court ruling found that Congress had not formally given the FDA authority to regulate tobacco products; thus, oversight was returned to Congress, though the responsibility was not efficiently managed during this time period.{5} The Tobacco Control Act, on the other hand, significantly reigned in the tobacco market and provided safeguards to protect the welfare of general public.

### **The Beginning of ENDS**

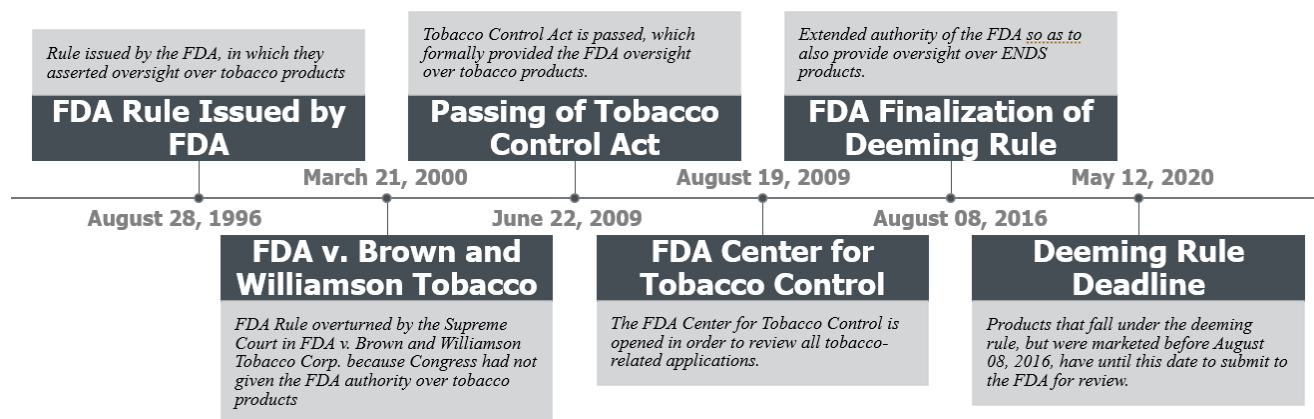
The Tobacco Control Act provided general direction for the regulation of cigarettes but did not go beyond the purview of what was already in the market. Because of this, the market shifted to give rise to the next generation of tobacco products in the form of ENDS devices, also known as e-cigarettes.

ENDS are nicotine products that are generally composed of an electronic heating element along with a liquid nicotine cartridge that is heated to form nicotine vapor for oral absorption.{6} With the passing of the Tobacco Control Act, cigarette regulations had been implemented, but overarching rules for ENDS development and marketing had largely been ignored or were never discussed.

The FDA had to set a standard for providing oversight of ENDS, so in 2016, the agency drafted guidance by which to regulate ENDS products under the Tobacco Control Act.{7} This Deeming Rule, which deemed all tobacco and ENDS products to be under the purview of the FDA, was made in response to the overwhelming increase in ENDS in the market. In summary, the Deeming Rule imposed a stop on independent manufacturing of ENDS and their associated cartridges (see Figure 1 for a timeline of important events related to tobacco legislation).

Additionally, any tobacco product on the market prior to February 15, 2007 would be grandfathered into the market, but products marketed after this date would require FDA approval. There was some leniency—products that were on the market before August 8, 2016 that were not grandfathered in would be subject to the FDA policies and could continue to be marketed, but were required to be submitted for review no later than May 12, 2020. Failure to meet this deadline would result in a product’s removal from the market. A draft guidance was provided to industry but was not finalized until June 2019.

**Figure 1: Timeline of Major Events in Tobacco Regulation History**



### Pre-Market Approval Process Overview

In many respects, the review and approval processes for ENDS devices are very similar to the rules for the FDA medical device regulatory pathways. There are three methods by which new ENDS products can be approved (see Table 1 for summary).

The *Pre-Market Tobacco Application* (PMTA) asks manufacturers to demonstrate that a new product would be “appropriate for the protection of the public health.” The purpose of a PMTA is to provide scientific data that support this endeavor by demonstrating the risks or benefits of the device as a whole, whether people who use or don’t use tobacco products would be more or less likely to use them given the existence of the new product, and the use of appropriate controls and manufacturing processes in making the product.

The *Substantial Equivalence* (SE) pathway is intended for tobacco products that may be found “substantially equivalent” to a predicate product, or if there are some differences, demonstrating that the new product does not raise new concerns for public health versus the predicate.

The *Substantial Equivalence Exemption* (EX) pathway is for tobacco products that have already been approved. These products would have to be modified by adding or deleting a tobacco additive, or by increasing or decreasing the quantity of tobacco featured.

For the purposes of this paper we will only be looking at the PMTA pathway, as most ENDS products will not have already received approval, and as such, will not have a predicate device available which would allow for any SE submission.

**Table 1: Tobacco Product Approval Pathways**

<b>Approval Pathway</b>	<b>Purpose</b>	<b>Products Allowed in Pathway</b>	<b>Time from Submission to FDA Response</b>	<b>Similarity to Device Approval</b>
Pre-Market Tobacco Application (PMTA)	Demonstrate that a new, never approved, tobacco product would be appropriate for the protection of public health	Any new tobacco product marketed after 2/15/2007	180 days	Pre-Market Approval
Substantial Equivalence (SE)	Show equivalence to a predicate product that has already received approval from the FDA	Any product that has received PMTA approval or was marketed before 2/15/2007	90–180 days	510(k) Application
Substantial Equivalence Exemption (EX)	Pathway for products that are modified by adding/deleting tobacco additive or increasing/decreasing quantity of tobacco	Any product that has received PMTA approval or was marketed before 2/15/2007	90 days	Device Class I Exemption

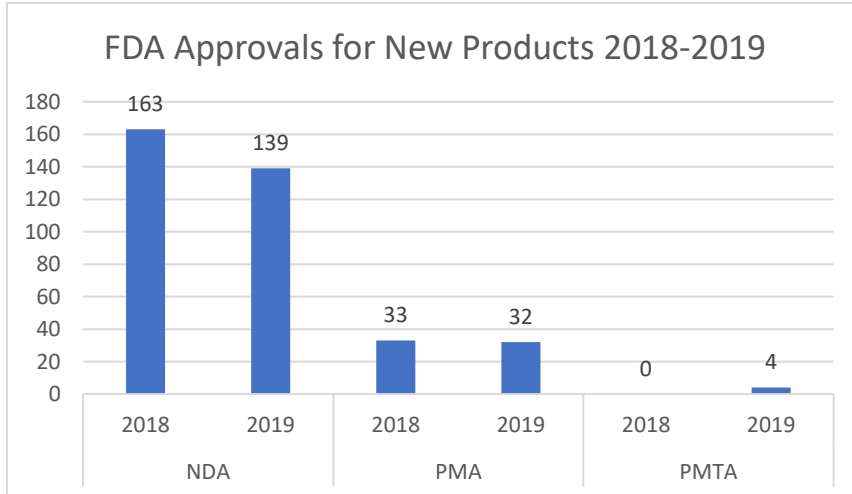
## Methods

Data were obtained from FDA online archives of all PMTA packages from industry and the resulting marketing decisions. PMTA submissions were reviewed and compared to New Drug Applications (NDAs) and Pre-Market Applications (PMAs) over a two-year period (January 2018 through December 2019). Analyses were performed in March 2020.

## Results

ENDS device submissions to the FDA had not really advanced to the PMTA level until fairly recently. Over a two-year period, only four ENDS products were approved by the FDA. In comparison, more than 350 new drugs and devices had been approved in that same timespan. (see Figure 2).

**Figure 2: FDA Approvals for New Products via New Drug Application (NDA), Pre-Market Approval (PMA), and Pre-Market Tobacco Approval (PMTA)**



*Data sources:* [www.fda.gov/drugs/nda-and-bla-approvals/nda-and-bla-calendar-year-approvals](http://www.fda.gov/drugs/nda-and-bla-approvals/nda-and-bla-calendar-year-approvals), [www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm](http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm), and [www.accessdata.fda.gov/scripts/fdatrack/view/track.cfm?program=ctp&id=%20CTP-OS-total-PMTA-since-Program-Inception](http://www.accessdata.fda.gov/scripts/fdatrack/view/track.cfm?program=ctp&id=%20CTP-OS-total-PMTA-since-Program-Inception).

## **Discussion**

The regulatory approvals for new tobacco products are in its infancy. As stated previously, FDA guidance was finalized as recently as November 2019, and any new products to be marketed after May 2020 require FDA approval. Compared to drugs and devices, the pool of products that will need a PMTA is fairly small.

As seen in Figure 2, only four ENDS products have been approved for marketing through the PMTA process in the U.S. since 2018. In comparison, there are many more approved applications for medical devices and drugs during that same time span. Although there obviously is no equivalency between the three categories, considering that the deadline for review of existing tobacco products was May of this year, there should be a sense of urgency from the tobacco industry to meet the demands of smokers in the U.S. There will be a huge windfall of banned e-cigarettes in the market at this rate, because any unapproved tobacco products will be taken off the shelves.

These regulations have had an impact on the tobacco industry, in that they have effectively relegated innovation within the field of tobacco science to larger companies. Smaller companies will have a much harder time breaking through and competing with larger companies. {8} New tobacco companies will have to be developed more in line with other drug and medical device conglomerates. Cessation of nicotine addiction is a lofty goal; it will only be harder to achieve if the development of potential solutions is stonewalled due to lack of resources.

## **Conclusion and Future Considerations**

It is a great step forward that these products are now regulated under the FDA. The previous system was difficult to manage and varied from state to state. Rather than ensuring the safety of the public, the previous system had only considered interstate trade. The new system in place ensures that all tobacco products are thoroughly reviewed prior to marketing. There are potential concerns with the effect the regulations will have on smaller tobacco companies; however, the protection of the general welfare of the public must come first in the realm of tobacco products.

Innovation begets innovation—the tobacco industry is no exception. As the markets had shifted once already from cigarettes to ENDS, the market is once again shifting—this time from ENDS products to disposable e-cigarettes. These new, disposable nicotine products are not that different from the current ENDS products—the only difference between the two is the intended use.

ENDS products are intended to be used multiple time, with users only having to put in a new cartridge every time they want to vape. In contrast, the new format of disposable nicotine devices offers the same safe route of administration as the ENDS products but is only intended to be used once and disposed of. The current regulations only cover ENDS with refillable cartridges, so exploration of how the regulations affect the newer products is needed.

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