



Reading the Tobacco Leaves: Paths and Challenges for a Nicotine Reduction Rule

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Paths and Challenges for a Nicotine Reduction Rule

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Speakers

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Financial Disclosures

PinneyAssociates provides consulting services on tobacco harm minimization to Juul Labs, Inc.

Within the past three years, PinneyAssociates has consulted for British American Tobacco and Reynolds American, Inc and subsidiaries on tobacco harm reduction.

FDA's Comprehensive Plan for Tobacco and Nicotine Regulation

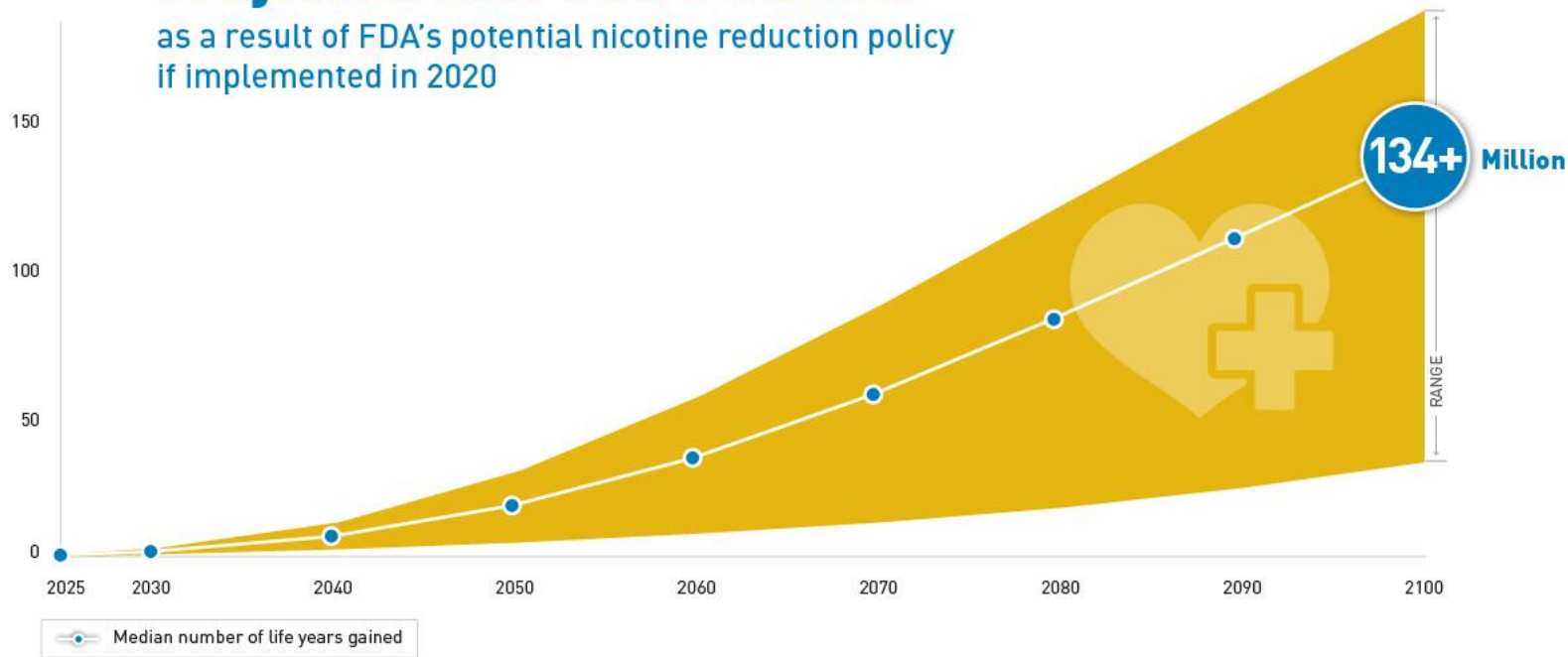
- Lowering nicotine in cigarettes to a minimally- or non-addictive level
- Provide an array of noncombustible alternatives for those who need or want to continue using nicotine
 - Nicotine replacement therapies
 - Consumer nicotine and tobacco products (including e-cigarettes)
- Push-Pull strategy to move smokers from smoke to noncombustible sources of nicotine



FDA's Population Modeling – a Look at What Could Be

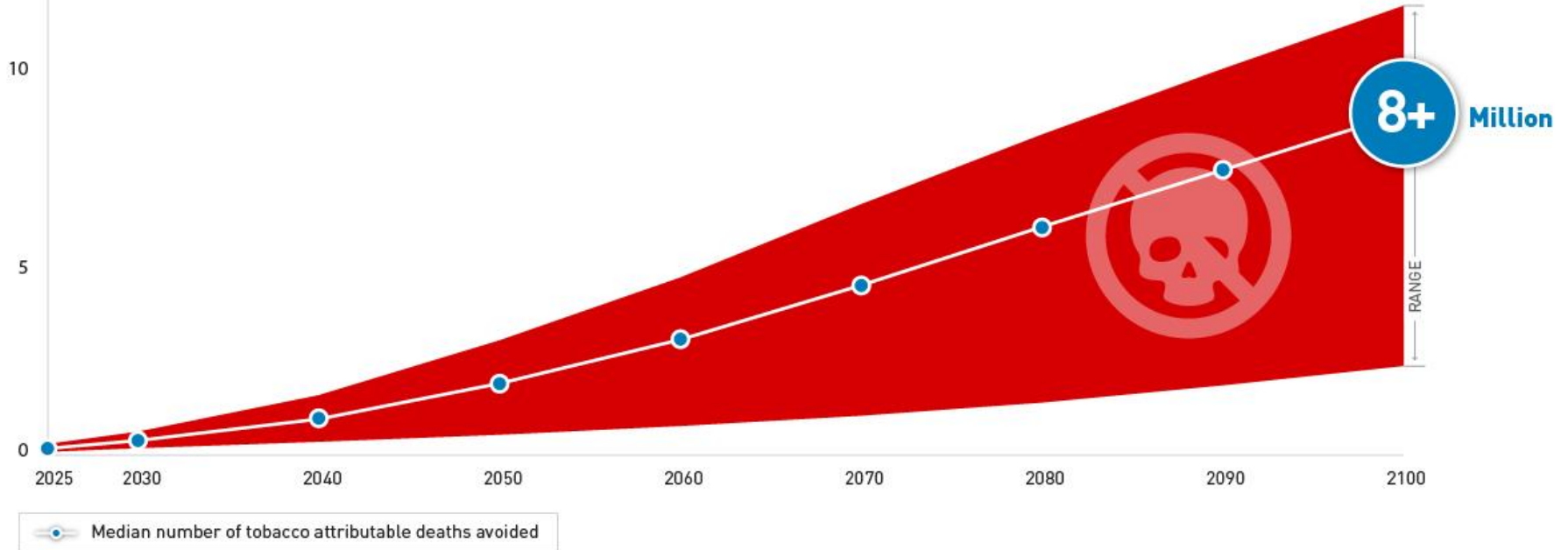
Projected Life Years Gained

as a result of FDA's potential nicotine reduction policy
if implemented in 2020



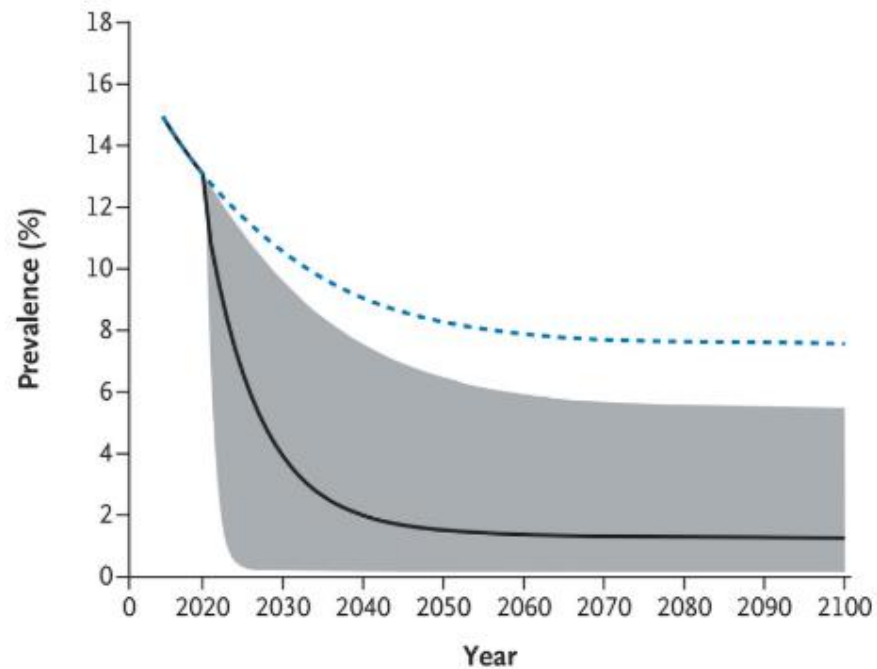
Projected Tobacco Attributable Deaths Prevented

as a result of FDA's potential nicotine reduction policy
if implemented in 2020

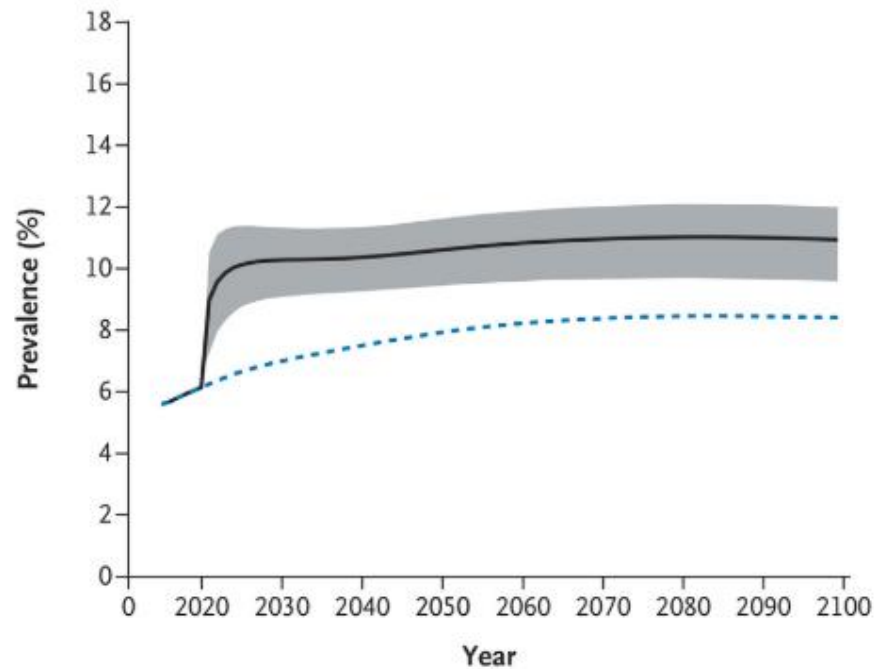


--- Baseline scenario ■ Policy scenario: 5th to 95th percentile — Policy scenario: Median

A Cigarette Smoking



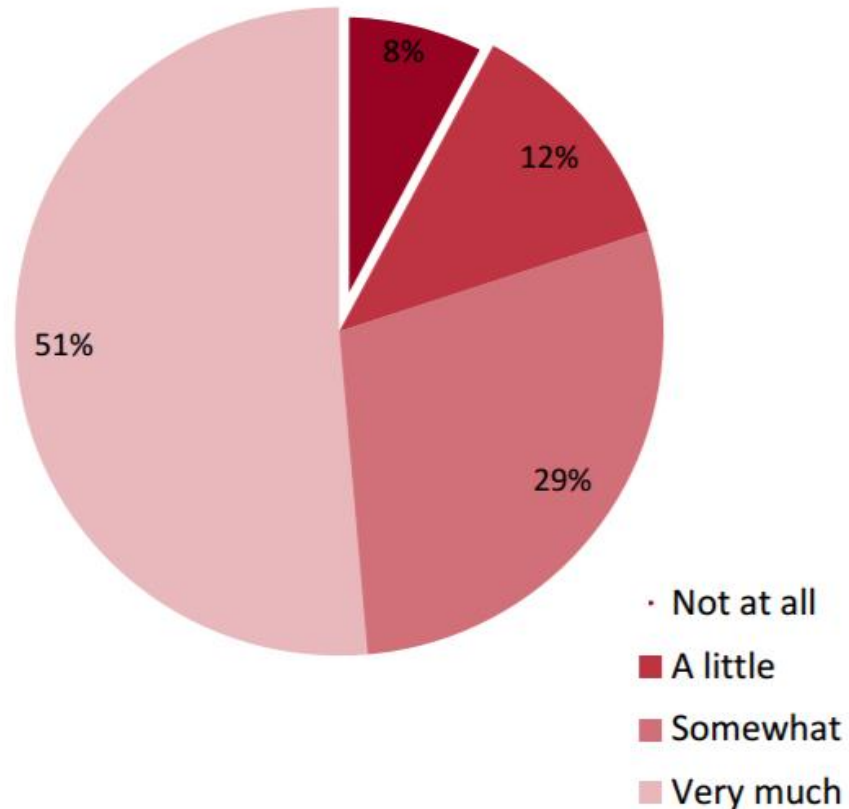
B Noncombusted Tobacco Use



PATH STUDY FINDINGS: NICOTINE AND CANCER

To what extent, if at all, do you believe the nicotine in cigarettes to be the chemical that causes most of the cancer caused by smoking?

The majority (80%) believe (*very much* or *somewhat*) that nicotine causes cancer.



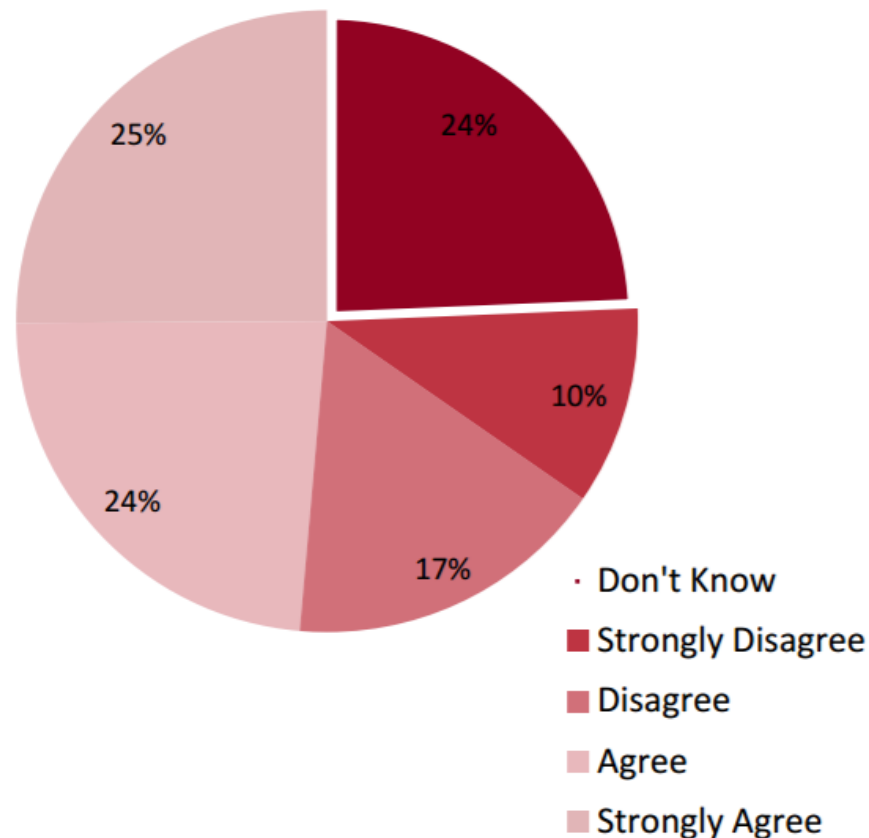
HINTS-FDA

FINDINGS: NICOTINE AND CANCER

The nicotine in cigarettes is the substance that causes most of the cancer caused by smoking.

Just under half (49%) agreed (*strongly agree* and *agree*) nicotine causes cancer.

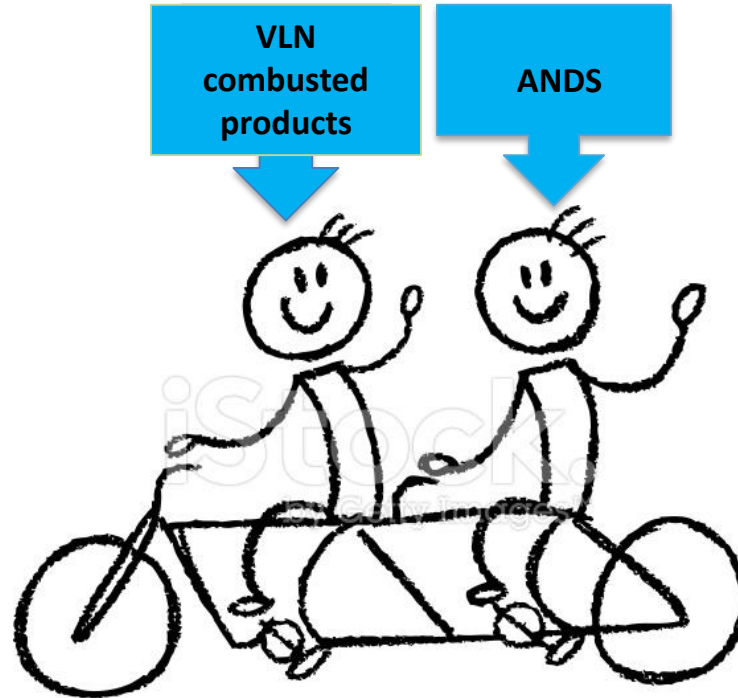
24% selected *don't know*.



Warner and Schroeder – JAMA Commentary

“A first order of business for FDA’s continuum-of-risk based plan, as well as for all governmental and on governmental health organizations should be honest public education about the relative risks of different tobacco and nicotine products, along with education about the role of nicotine in tobacco-related disease. The **public needs to understand that tobacco smoke—not nicotine—is the cause of smoking related mortality and morbidity.**”

Tandem Effort



Benningfield, 1994 Russell, 1991

ANDS

Meds

VLNC





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Stacey Gagosian

Managing Director, Public Policy

Effects of Nicotine

Effects of Nicotine

- Addiction

““To lower nicotine too much might end up destroying the nicotine habit in a large number of consumers and prevent it from ever being acquired by new smokers.” -- 1959 BAT Document

- Youth/Developing Brain

- From the 2014 Surgeon General Report: Nicotine Impacts “fetal growth and development, immune function, the CV system, the central nervous system and carcinogenesis.”

Strongly Support Reducing Nicotine Levels

Nicotine's Impact on Public Health

- Nicotine is the main reason people smoke
- Industry has manipulated nicotine levels and the other ingredients in cigarettes to make them even more addictive

Reducing Nicotine Levels Will Benefit Public Health

- Prevent youth and young adults from initiating and becoming addicted to tobacco

FDA modeling: 16 million youth and young adults who otherwise would have started smoking would not do so.

- Encourage Smokers to Quit

FDA modeling: An additional 5 million smokers would quit.

What is needed to realize the benefits of VLNC

Product Standard Details and Application

- The level of nicotine allowed should be non-addictive
- The product standard must apply to all combustible products

Significant Public Education

- Reduced-Nicotine Products are not safer than current products
- Misperceptions about nicotine are rampant
 - Many people are confused about nicotine's role in disease and addiction – that needs to be corrected

Alternatives to Cigarettes

- FDA needs to encourage development of new and effective cessation interventions that are available to all who need them
- Fully reviewed and well-regulated, less harmful alternatives may be useful to help people switch completely from VLNC as they transition to quitting.

This is NOT true in the current regulatory situation
Alternatives should have reduced nicotine as well

Illicit Market

- Little evidence that a black market for modified cigarettes exists or will be developed
 - For one to exist, a large-scale smuggling operation or illegal domestic production would be needed – neither is likely
- The development of a black market is not a reason to not institute strong policies – such as VLNC standard
 - Underage youth tobacco use is the most important illicit market but no one says we shouldn't have youth sales bans
- The existence of an illicit market does not cancel out the public health benefit

Conclusion

Nicotine in combustible tobacco is highly addictive and the reason that people smoke. A product standard reducing nicotine levels to non-addictive levels will improve public health by encouraging current smokers to quit and preventing non-smokers from taking up smoking in the first place. While this must be done in conjunction with other regulatory measures, the impact of such a product standard is truly staggering.

thank you

truthinitiative.org



An FDA- mandated Product Standard for Reduced Nicotine Content Cigarettes: How Might It Be Challenged?

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The content of this presentation is solely the responsibility of the author and does not necessarily represent the views of the NIH, FDA, or any other funding agency.

JF has done paid consulting for pharmaceutical companies involved in developing and marketing smoking cessation products (e.g. Pfizer, GSK) and has received a grant and study product from Pfizer.

JF has not done paid work of any sort for tobacco or e-cig manufacturers.

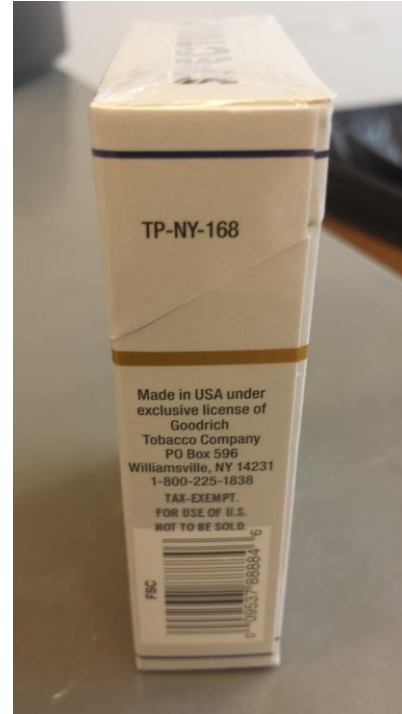
- **The 2009 Family Smoking Prevention and Tobacco Control Act gave FDA the authority to regulate tobacco products.**
- **The act explicitly gave FDA the power to reduce or take out any chemical in cigarettes, except for nicotine, which could not be reduced to zero.**
- **However, in order to make such changes in the form of a new product standard, FDA must demonstrate, via evidence, that the new product standard is feasible and will result in a net improvement in public health.**

- **The outcome of these legal challenges will depend, at least partly, on the evidence FDA can present on the likely public health impact of a reduced nicotine standard for cigarettes.**
- **A large part of the evidence base on which FDA would rely on in court includes the evidence produced in research projects evaluating the effects of reducing the nicotine content in cigarettes or other nicotine delivery products.**
- **The aim of this presentation is to highlight some of the ways the industry may challenge our research, and to show what existing evidence we already have.**

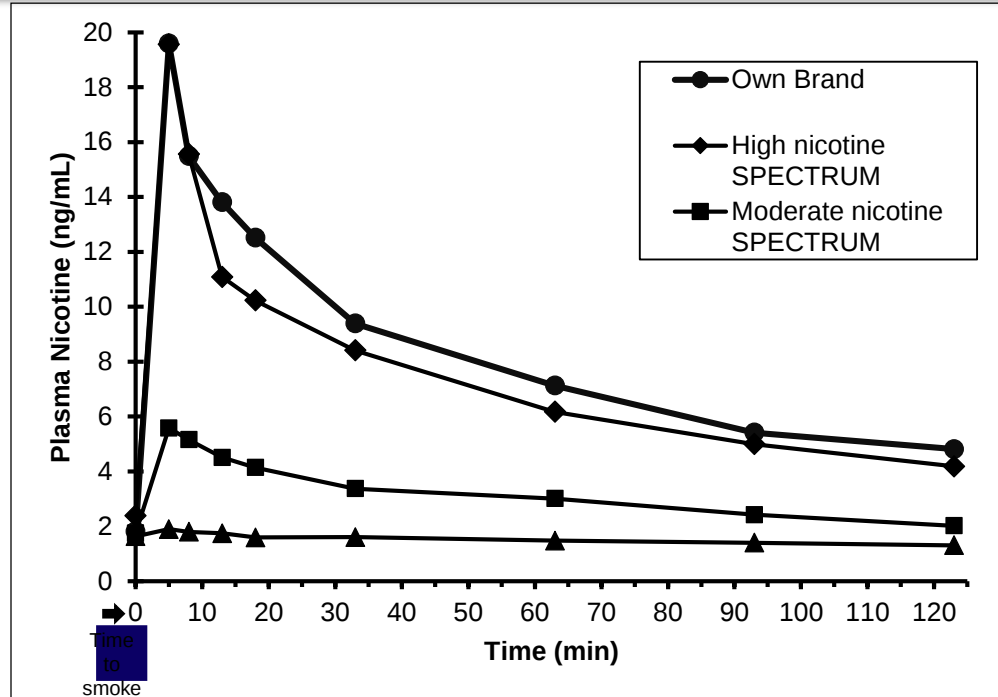
- **Our current studies include smokers switching to research cigarettes containing nicotine levels as low as 0.3mg/cig (as compared to a typical nicotine content of 10-16 mg/cigarette in popular cigarettes).**
- **So this lowest level of nicotine content that is currently being studied involves cigarettes containing around 2-4% of the nicotine content of commercial cigarettes, or a 97% reduction.**
- **Although these cigarettes contain nicotine, industry lawyers may argue that although this very low level is within the letter of the law, it is not within the spirit of the law as intended by Congress.**

-

Spectrum Research Cigarettes



**Mean plasma nicotine (ng/ml) from smoking single own brand, NRC600, NRC400 or NRC102
Spectrum research cigarette (n=12) Kamens et al, 2019**
Nicotine boost on “very low” = +0.3 ng/ml. $p < 0.05$



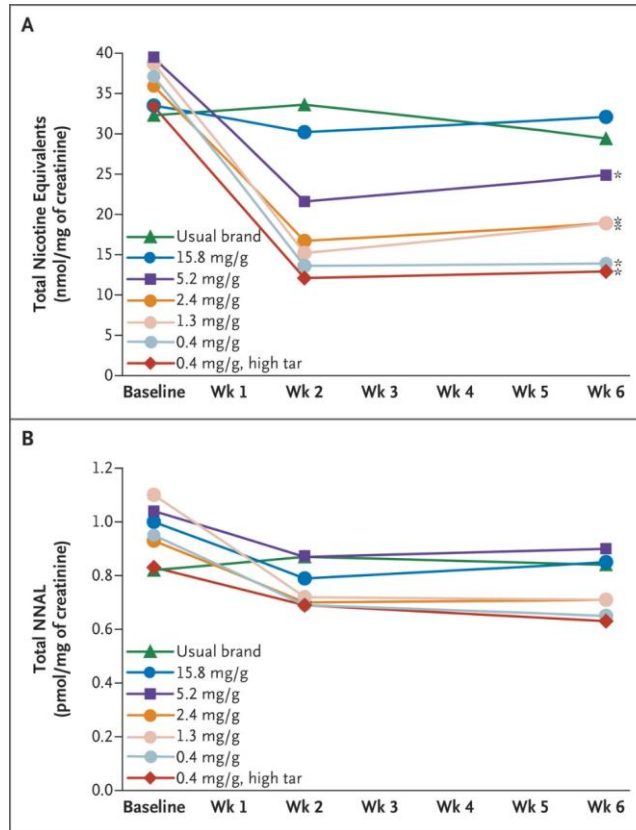
Conclusion: Cigarettes with 97% lower nicotine content still deliver nicotine.

- Most of the human research relevant to a reduced nicotine content Product Standard has made use of specially manufactured SPECTRUM Research Cigarettes supplied by the NIDA Drug Supply Program.
- These research cigarettes come in a limited number of varieties (and a single length) and genetic engineering enables manipulation of the nicotine content. **However, tobacco companies may claim that results of trials based on switching to SPECTRUM cigarettes are not relevant to their brands because they are “different” or superior in some important ways** (e.g. compensatory smoking may not be observed with reduced nicotine SPECTRUMS because smokers don’t like smoking them).
- In order to assess this potential problem we asked 341 smokers to provide a wide variety of measures during a baseline week smoking their own brand and then after 2 weeks of smoking SPECTRUM normal nicotine content (11.6mg/cig) cigarettes, and also to state whether they would pay for SPECTRUMS and decide whether to continue smoking SPECTRUMS in an 18-week trial.

- **67% rated the SPECTRUM cigarettes as good as or better than their own brand cigarettes.**
- **95% of participants chose to continue smoking SPECTRUMS for the 18-week randomized trial.**
- **CONCLUSION:**

Both menthol and non-menthol SPECTRUM research cigarettes appear to be acceptable to smokers.

Biomarkers of Exposure to Nicotine and 4-(Methylnitrosamino)-1-(3-Pyridyl)-1-Butanone (NNK) According to the Nicotine Content of Cigarettes.



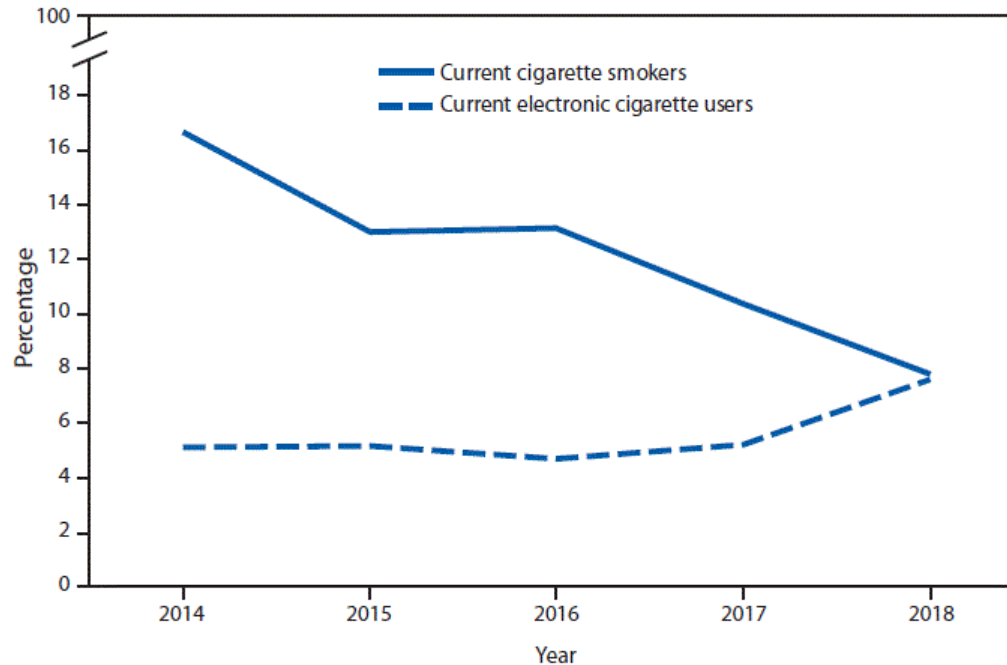
Reducing nicotine content per cigarette could cause smokers to inhale more toxicants by smoking more cigarettes or more smoke per cigarette “compensatory smoking”.

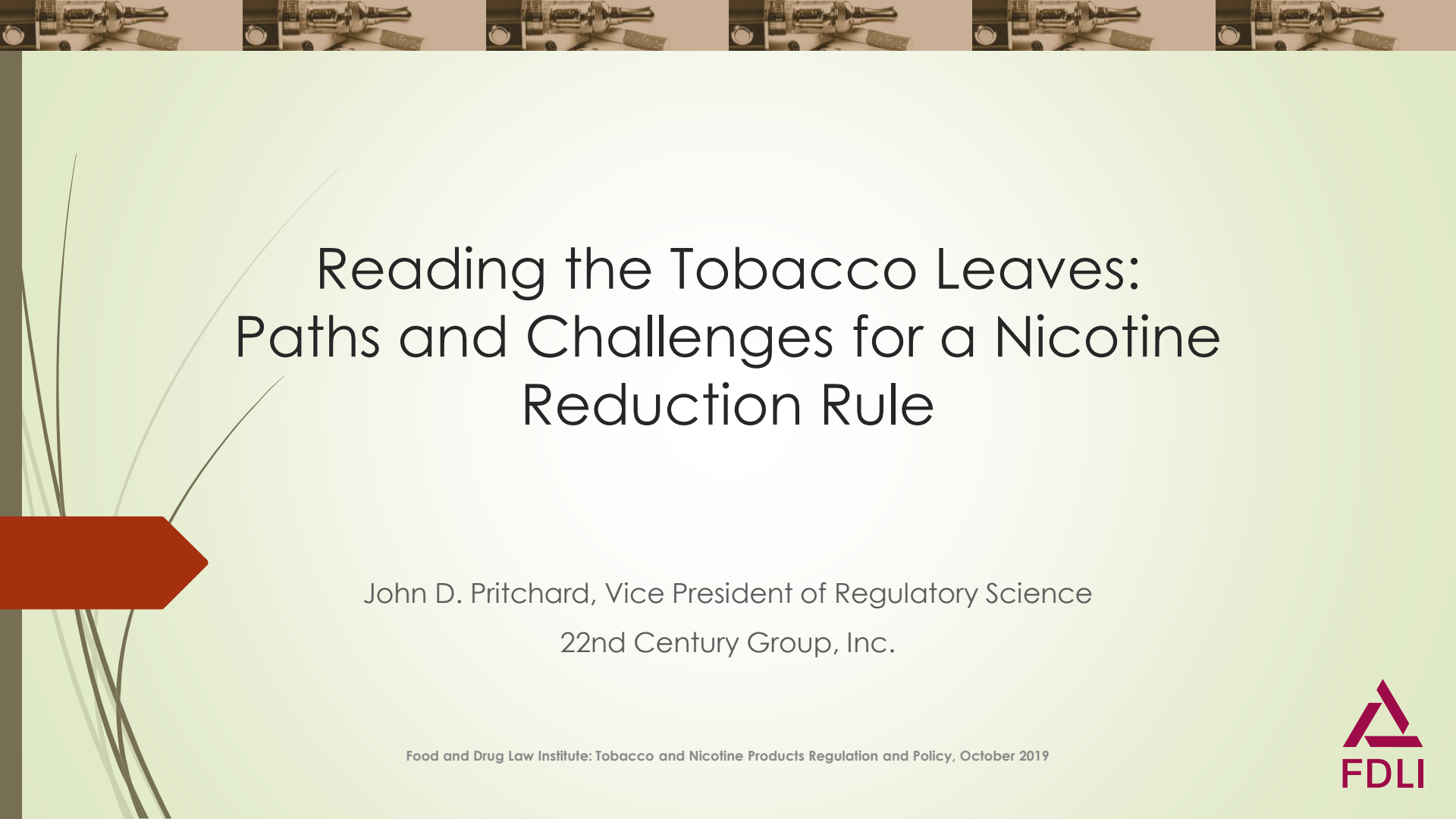
CONCLUSION

No evidence in this trial or other similar ones that when smokers switch to VLNCs they “compensate” by inhaling more smoke (i.e. toxicants) in order to get more nicotine out of each cigarette.

On the contrary, at very low nicotine content levels, smokers smoke fewer cigarettes and inhale less smoke

- **FDA SHOULD MOVE FORWARD ASAP. By the time this goes through the courts, e-cigs may have largely replaced cigarettes.** From 2014 to 2018, the percentage of adults aged 18–24 years who currently smoked cigarettes decreased from 16.7% to 7.8%. The percentage of adults in this age group who currently used electronic cigarettes increased from 5.1% to 7.6%. **Source:** National Health Interview Survey, 2014–2018 data. <https://www.cdc.gov/nchs/nhis.htm>.





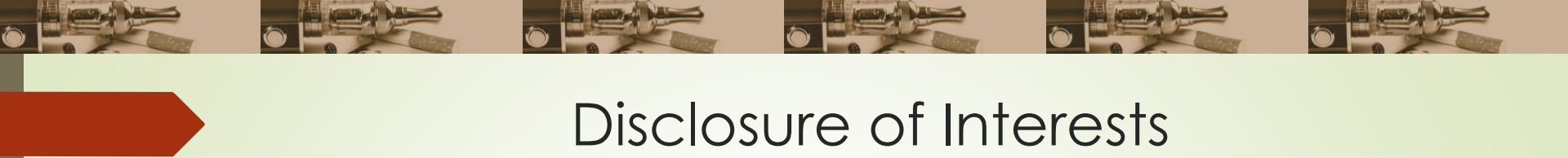
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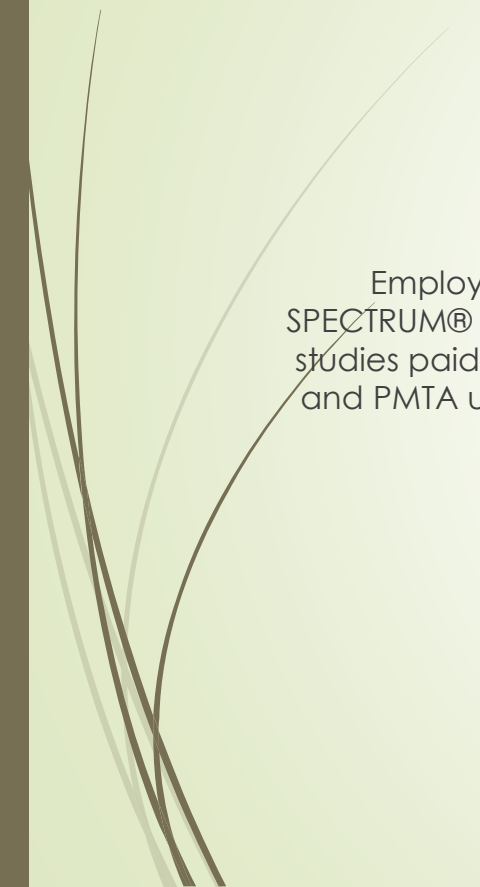


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Disclosure of Interests



Employee of 22nd Century Group, Inc., which has provided over 25 million proprietary SPECTRUM® research cigarettes that have been used in approximately 100 independent clinical studies paid for by U.S. Federal Government agencies. 22nd Century Group also has an MRTPA and PMTA undergoing substantive scientific review by FDA for combustible tobacco cigarettes containing 95% less nicotine than conventional cigarettes.



Tobacco Product Standard for Nicotine Level of Combusted Cigarettes

- **2009** Family Smoking Prevention & Tobacco Control Act signed into law, having passed both Houses with overwhelming bipartisan support
- **2017** *"FDA announces comprehensive regulatory plan to shift trajectory of tobacco-related disease, death"*
- **2018** ANPRM: Tobacco Product Standard for Nicotine Level of Combusted Cigarettes Published in the Federal Register
- **2019** In an interview, then FDA Commissioner Gottlieb commented *"I would expect the notice of proposed rule making would be out [of FDA, to HHS] later this summer"*
- **2019** CDC reports 2018 Study: 80% of US Adults, including 80% of people who smoke, favor lowering nicotine levels in cigarettes
- **2019/20** NPRM expected to published in the Federal Register

[https://www.gjpmonline.org/article/S0749-3797\(19\)30210-7/fulltext](https://www.gjpmonline.org/article/S0749-3797(19)30210-7/fulltext)

<https://www.c-span.org/video/?458890-1/outgoing-fda-commissioner-scott-gottlieb-speaks-brookings-institution>

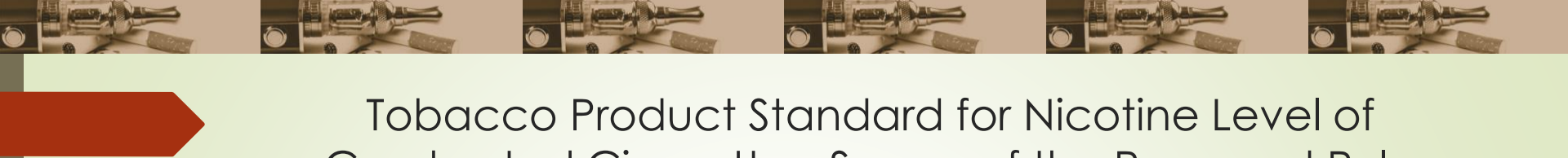
<https://www.fda.gov/news-events/press-announcements/fda-announces-comprehensive-regulatory-plan-shift-trajectory-tobacco-related-disease-death>

<https://www.reginfo.gov/public/do/eAgendaViewRule?pubid=201904&RIN=0910-AH86>



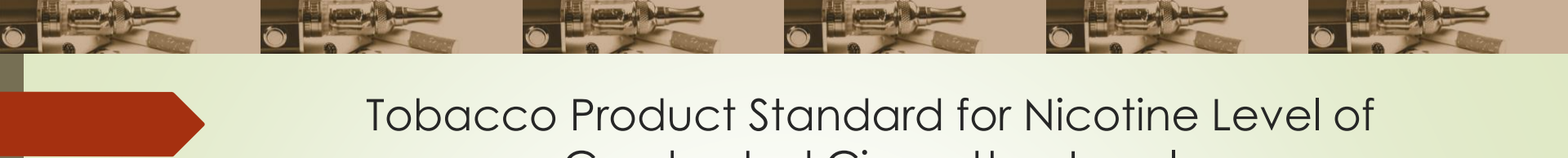
Tobacco Product Standard for Nicotine Level of Combusted Cigarettes: Overview

- The Scope of the Proposed Rule: Covered Products and their Prevalence and Initiation Rates
 - Rationale for Developing A Standard for Nicotine & Why the Standard is Appropriate for the Protection of Public Health, as required by the Act
 - Information on Technical Achievability
 - Description of Proposed Regulation; Product Requirements i.e. The Nicotine Level, Description of Analytical Methods
 - Implementation & Proposed Effective Date
- 



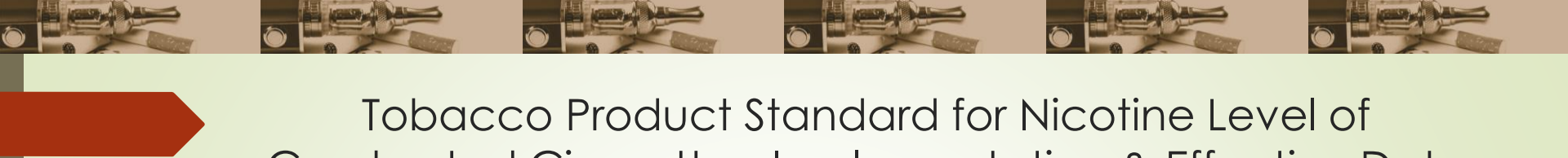
Tobacco Product Standard for Nicotine Level of Combusted Cigarettes: Scope of the Proposed Rule

- **Cigarettes:** Tobacco Product category that causes the greatest burden of harm to public health given prevalence of cigarette use, including among youth, toxicity, addictiveness and resulting death and disease
- Its foreseeable that other products currently on the market including **“Little Cigars”, Cigarillos, Roll-your-own tobacco, pipe tobacco**, etc. would also feature in the standard or may become the subject of further regulation.
- **Heated Tobacco.** FDA has recently authorized a non-combusted cigarette, consequently this will not be covered by the standard; FDA has also stated, “Available data, while limited, also indicate that few non-tobacco users would be likely to choose to start using IQOS, including youth.”



Tobacco Product Standard for Nicotine Level of Combusted Cigarettes: Level

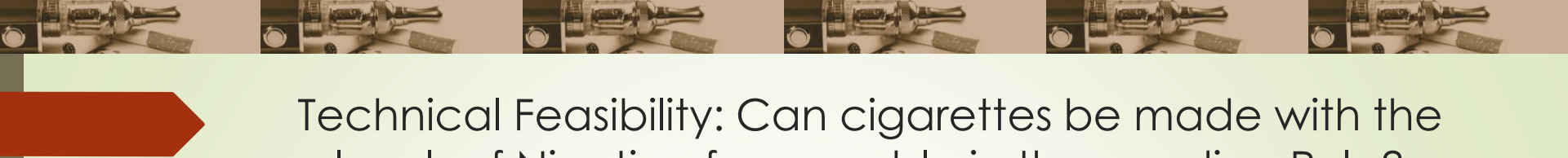
- FDA has publicly stated that they are looking at a nicotine level between 0.2 mg-0.7mg/g tobacco, with particular interest on 0.3, 0.4 and 0.5 mg/g.
- Thus the standard could read “...FDA is proposing that the **Maximum Nicotine Level of tobacco filler must not exceed 0.5 milligrams per gram of tobacco (on a dry weight basis)**...”
- A further FDA statement is likely to provide a ceiling on total nicotine within the product, potentially on a per stick basis, to prevent product modifications that work against the public health impact of the standard



Tobacco Product Standard for Nicotine Level of Combusted Cigarettes: Implementation & Effective Date

- **Implementation** – Likely a single target, where the standard will be implemented in a **one-time reduction from current levels to the new product standard**; recent independent clinical studies support this path rather than a gradual reduction over time
- **Effective Date.** FDA has substantial latitude in making its determination
 - “..effective date of that product standard **shall be not less than 2 years** after the date of publication of the final regulation establishing the standard.” [TCA]
 - Based on FDA’s evaluation of comments and other data potentially “...**effective 3 years after the date of publication of the final rule**...would allow adequate time for any necessary changes to achieve the Nicotine level...”.

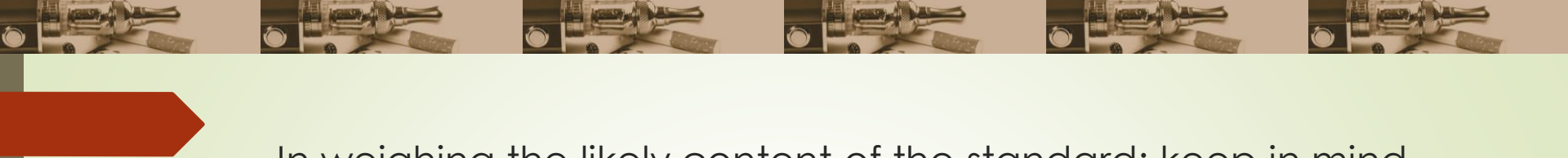
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6372240/>



Technical Feasibility: Can cigarettes be made with the levels of Nicotine foreseeable in the pending Rule?

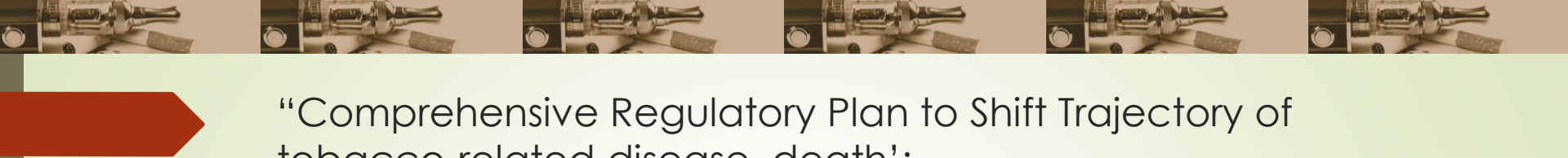
- “Every significant achievement in tobacco control was preceded by many influential people saying it couldn't be done, wouldn't work, or would create new problems” Ruth Malone, RN, PhD, FAAN
- Good News. Yes, it's already been done. Multiple varieties of low nicotine tobaccos are already developed; **Non-GMO Flue Cured Bright/Virginia and Burley tobaccos have been cultivated in multiple sites in US tobacco growing regions**, further varieties are in advanced development
- **Other alternative approaches, including extraction, became available and were used decades ago to mass produce millions of low nicotine cigarettes**

Malone, R. (2013). Tobacco endgames: what they are and are not, issues for tobacco control strategic planning and a possible US scenario. Tobacco Control, 22(suppl 1), pp.i42-i44.



In weighing the likely content of the standard; keep in mind that the FDA knows this...

- “If cigarette smoking continues at the current rate among youth in this country, **5,600,000 of today’s Americans younger than 18 will die early from a smoking-related illness.** That’s about 1 of every 13 Americans aged 17 years or younger who are alive today.¹” – CDC “Youth and Tobacco Use”



“Comprehensive Regulatory Plan to Shift Trajectory of tobacco-related disease, death’: A Lesson and Inspiration from Public Health History

- Smoking cigarettes kills millions of people each year, as smallpox did for many hundreds of years. However, with concerted efforts, smallpox was eradicated in North America in 1952 and around 25 years later, the disease was *globally eradicated*
- On June 22, 2009, the Family Smoking Prevention and Tobacco Control Act gave the United States Food and Drug Administration authority, in the interest of public health, to lower the amount of nicotine in cigarettes to any level above zero
- **This authority has set North America on a path to again become the first continent to consign a different cause of millions of deaths to history, by simply making cigarettes minimally or non-addictive**

<https://www.who.int/csr/disease/smallpox/en/>

<https://www.cdc.gov/smallpox/pdfs/smallpox-eradication-map.pdf>