Premarket Applications and the Element of Uncertainty

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Assessing CTP Documents to Reduce Uncertainty and Gain Insights

Jim Solyst, Swedish Match

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Key Points

- There will always be some uncertainty
- Uncertainly will reduce as more decisions are made
- CTP decision documents, proposed rules, and briefing documents provide insight
- Example: references to GOTHIATEK in CTP documents
- How does that impact the regulatory environment?

Uncertainty

- Uncertainty is part of the federal regulatory process
- CTP is still evolving; FDA commitment is more clear (Dr. Gottlieb is the first FDA Commissioner since 2009 to embrace the nicotine debate)
- No track record: essentially one PMTA and no MRTPAs
- “Foundational rules” will be helpful but not as helpful as decision documents

Examples of Useful CTP Documents

- Decision documents: Technical Project Lead (TPL) for the Swedish Match General snus PMTA decision.
- Proposed products standard: NNN in Smokeless
- FDA Briefing Document for the Camel snus TPSAC
- What do they have in common? GOTHIATEK

GOTHIATEK

- Pertains to Swedish Match snus
- Relevant to all Swedish Match products: others smokeless products and ZYN
- Comprehensive
- CTP is most interested in the Harmful and Potential Harmful Constituent (HPHC) component

PMTA Technical Project Lead Report

- Cites three reasons why a PMTA was awarded: low HPHCs, particularly NNN, and
- GOTHIATEK, which is listed first:
- “Produced with a voluntary, proprietary standard using acceptable manufacturing processes as confirmed by both application review and on-site inspections.”
- Messages: A PMTA should have low NNN and other HPHCs and it is important that a company has an internal standard (product standard)

Proposed NNN in Smokeless Rule

- “This proposed product standard would require that the mean level of NNN in any batch of finished smokeless tobacco products not exceed 1.0 microgram (µg) of NNN per gram of tobacco …”
- How does CTP justify the proposed rule?
- “Manufacturer awareness of the NNN content in their products is evidenced by some manufacturers adopting voluntary industry quality standards that directly limit quantities of carcinogens (including NNN) in Sweden, such as Swedish Match’s GothiaTek standard.”

FDA Briefing Document for the Camel snus TPSAC Meeting

- “Table 3. GothiaTek® standard limits compared to 95% confidence interval levels of constituents in Camel Snus (Data Source: Section 7.1.2 of the MRTPAs)”

What Does This Mean? Is this a Good Thing?

- It means that CTP has indicated/implied that GOTHIATEK serves as a de facto CTP product standard.
  - CTP relying on an existing company standard is a good thing;
  - Acknowledging that a company has a standard is a good thing;
  - But CTP needs to understand that GOTHIATEK was developed over time and applies to snus.
- Update to the Swedish Match article cited in the FDA Briefing Document: Rutqvist, Ljung, and Lindholm

Continued

- At one time (late 2016-January 2017) CTP wanted the HPHC (NNN) component GOTHIATEK to apply to all smokeless products
- It is not a good thing if a low NNN product like moist snuff is not allowed on the market.
- It is not a good thing if a company has to comply with a CTP administrative process in addition to meeting its own internal product standard;
- It is not a good thing if there is a negative impact on US tobacco growers.

Broader View

- Does the GOTHIATEK example mean that CTP is open to using industry standards?
- If so, how should the process work?
- Should CTP merely pull information from a company web site or article?
- Or should CTP engage with the company, seeking more full understanding.

Premarket Applications and the Element of Uncertainty

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CURRENT CHALLENGES

- Commissioner's objective of an efficient and transparent program
  - No opportunities for collaborative discussions
    - Applicants must respond to deficiency letters in abbreviated time frames, sometimes with additional testing, with no opportunity to substantively discuss with the Office of Science
    - Leads to additional deficiencies and ultimately NSEs based on FDA's "three cycle" review policy

CURRENT RESOURCES

- FDA Website
- TPL of PMTA, SE and Exempt Orders
- MRTPA information
- FOIA, Reviewer Manuals

WHAT CAN FDA DO?

- Vest manufacturers with the responsibility to determine whether a particular modification requires a premarket review (905(j)) submission
- Focus premarket review resources on the changes to tobacco products that truly raise different questions of public health
- Develop product class-specific guidance
- Cease using FDA premarket review as a substitute for current Tobacco Product Manufacturing Practice regulations
- Publish the Reviewer Manuals

POTENTIAL PATH FORWARD

- Provide TPL with P Find letters and afford expedited opportunity to meet
- Develop a Decision-tree approach (similar to FDA CDRH 510(k)) to allow certain changes for products on the market
- Provide product category-specific guidance

POTENTIAL PATH FORWARD

- Certain changes should be categorically exempt
  - Changes mandated by law
  - Changes implemented by third-party vendors that do not impact the manufacturer’s specifications for the tobacco product at issue
  - Product changes (physical parameters) that do not affect Tar/Nicotine yields

WHAT CAN WE DO?

- Absent an agreed and transparent approach, tobacco regulators and industry:
  - Use different formats, content and terminology in regulatory filings
  - Take different approaches in determining which product characteristics are most critical to a tobacco product’s quality, compliance and considerations on the impact on public health.

WHAT CAN WE DO?

- Result:
  - Same words used for different definitions confuses regulators
  - Attributes of a tobacco product appear to treated with the same criticality
  - No definition of ‘significant’
  - Loss of time, reputation and resources, for both regulators and industry
  - Diminished ability to prioritize & focus on products that truly raise different questions of public health.

WHAT CAN WE DO?

- Propose a standardized regulatory framework for tobacco products:
  - Standardized Product Guidelines & Glossaries, Table of Contents
  - A Tobacco Technical Document (similar to ICH CTD M4)

Premarket Applications and the Element of Uncertainty: Implications for Public Health Science

Ray Niaura, PhD

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FDLI, Washington, DC, Oct 25, 2018

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Disclosures (past 3 years)

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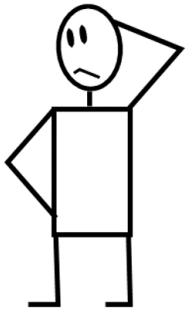
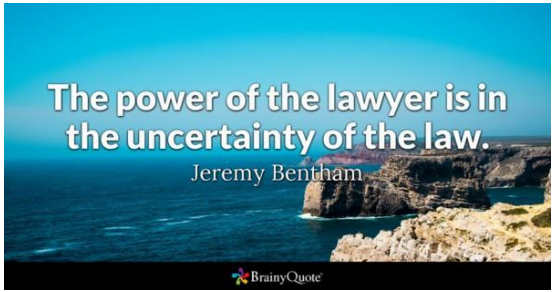
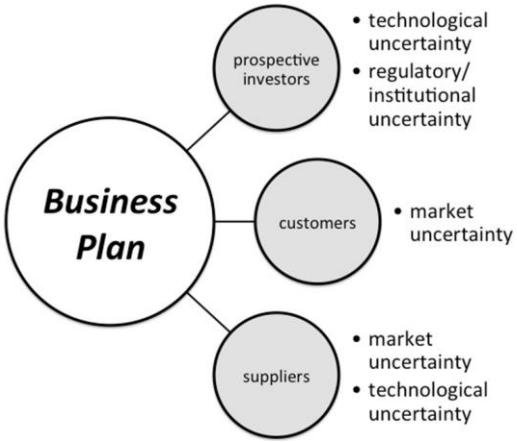
- Paid consultant to the Governments of Canada and USA via a contract with Industrial Economics Inc.
- Honorarium for a virtual meeting from Pfizer Inc.
- Red Sox fan

"Risk is measurable uncertainty"

"Uncertainty is unmeasurable risk"







Science-based regulation?

Opinions

We cannot let e-cigarettes become an on-ramp for teenage addiction

A man exhales smoke from an e-cigarette in Washington on Oct. 2. (Eva Hambach/AFP/Getty Images)

By **Alex M. Azar** and **Scott Gottlieb**
October 11 at 8:05 AM

Alex M. Azar is the secretary of health and human services. Scott Gottlieb is the commissioner of the Food and Drug Administration.

FDA Comments Cause Stock Market Uncertainty

October 1, 2018

Big tobacco companies have long been fearful of e-cigarettes cutting into their market as more smokers switch to vaping. Nonetheless, the FDA comments regarding the recent crack down on flavored e-liquids has sent tobacco stock prices soaring. Who is really benefiting from the latest attack on vaping?

Shares of the tobacco company Altria rose nearly 7% on Wednesday, marking their biggest one-day percentage increase since the financial crisis.

The equity market has spoken: in the wake of the FDA announcement, the tobacco majors recovered $20 billion of lost market cap in a single day, or 15% of the $137 billion lost since December 2017.

Center for Tobacco Products Overview

Improving Public Health

Our goal is to reduce the harm from all regulated tobacco products across the entire population, including:

- reducing the number of people who start to use tobacco products
- encouraging more people to stop using these products
- reducing the adverse health impact for those who continue to use these products

FDA's unique position as a regulatory agency allows for a framework of decision-making based on – and within the limits of – both the science and the law. For example, the law gives FDA the authority to adopt science-based product standards, which could require the reduction or elimination of an additive, constituent, or other component if doing so would be appropriate to protect public health.

CTP uses a comprehensive approach as the best way to end the negative health effects of tobacco use. This includes defining policy, issuing regulations, conducting research, educating Americans on regulated tobacco products, and making decisions on whether new products and claims can be marketed—including reviewing and evaluating applications and claims before the products are allowed on the market.

This cohesive, comprehensive approach can help us reach our goals of

- preventing people from starting to use tobacco products
- encouraging tobacco users to quit
- reducing the harm caused by tobacco use

As we work to protect the public's health, we will use the full power of the law to protect consumers from the dangers of tobacco use.

“For the first time, under the Family Smoking Prevention and Tobacco Control Act, the federal government, through the FDA Center for Tobacco Products (CTP), is able to bring science-based regulation to the manufacturing, marketing, and distribution of tobacco products.”

FDA Commissioner Margaret A. Hamburg, M.D.

September 19, 2013

The Importance of Tobacco Research

At CTP, we consider scientific findings in all our activities. Our unique position as a regulatory agency allows for a framework of decision-making based on – and within the limits of -- both the science and the law. Although a vast and sound science base already exists for many areas of the Tobacco Control Act, new research will build upon that robust base of scientific evidence. CTP has identified seven categories of research priorities:

- ***Product diversity*** – understanding the types of tobacco products and how their specific characteristics affect people's attitudes, beliefs, perceptions, and use of these products
- ***Addiction*** – understanding what effect different levels of nicotine and other factors have on addiction
- ***Toxicity and carcinogenicity*** – understanding how changes in tobacco products affect their potential for harm and ways to reduce that harm
- ***Health consequences*** – understanding the risks of different tobacco products
- ***Communication*** – finding ways to effectively convey information about the risks of using tobacco and about CTP's role in regulating tobacco products
- ***Marketing*** – understanding the impact of tobacco product marketing and public education on people's attitudes, beliefs, perceptions, and use
- ***Economics and policy*** – estimating the economic impact of CTP's regulations; also understanding how CTP's actions change tobacco use and illness and death from tobacco use

CTP relies on the most current science to make regulatory decisions on tobacco products. Scientific research is critical to our mission of reducing the death and disease resulting from tobacco use. Funding and supporting research will help us both write appropriate rules (regulations) and assess the impact of our rules and activities on public health.

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY A

Phil. Trans. R. Soc. A (2011) **369**, 4842–4852
doi:10.1098/rsta.2011.0174

Review

Risk, uncertainty and regulation

By John R. Krebs*

Jesus College, University of Oxford, Oxford OX1 3DW, UK

This paper reviews the relationship between scientific evidence, uncertainty, risk and regulation. Risk has many different meanings. Furthermore, if risk is defined as the likelihood of an event happening multiplied by its impact, subjective perceptions of risk often diverge from the objective assessment. Scientific evidence may be ambiguous. Scientific experts are called upon to assess risks, but there is often uncertainty in their assessment, or disagreement about the magnitude of the risk. The translation of risk assessments into policy is a political judgement that includes consideration of the acceptability of the risk and the costs and benefits of legislation to reduce the risk. These general points are illustrated with reference to three examples: regulation of risk from pesticides, control of bovine tuberculosis and pricing of alcohol as a means to discourage excessive drinking.

BioWorld
Actionable Intelligence • Incisive Analysis

FDA Faces Challenge of Dealing With Scientific Uncertainty

By Mari Serebrov

Washington Editor

WASHINGTON – Regulatory uncertainty at the FDA is often cited as a source of industry heartburn. But rather than turning down the heat, the agency is looking for ways to make that uncertainty less irritating, recognizing it as a natural part of the scientific process.

"Uncertainty is one of the more challenging things for people to understand," Jesse Goodman, the FDA's chief scientist, told the agency's Science Board Friday. "In fact, scientists don't seem to understand it."

The problem, he added, is that "uncertainty is not a concept that seems to be a part of our culture right now – except in celebrity marriages."

At the FDA, uncertainties inevitably arise when experts, using the same science, have conflicting interpretations and make different regulatory decisions. Instead of denying those uncertainties, Goodman said the FDA needs to do a better job of communicating them.

That idea is incorporated into the agency's new statement of key principles of scientific integrity. Founded on maintaining a firm commitment to science-based, data-driven decision-making free from political influence, the principles call for protecting and ensuring the accurate presentation of scientific data, including the underlying assumptions and uncertainties.

The new statement also requires a fair, transparent approach to resolving internal scientific disputes, carefully considering differing views.

OPINION

The FDA must resist the irrational fear of vaping

by Guy Bentley | August 07, 2018 11:52 AM

The FDA must recognize that while industry regulation is vital, control is deadly, and regulating too much can be just as lethal as regulating too little.
(Gabby Jones/Bloomberg)

Precautionary Principle

Preventive or corrective action to reduce or eliminate the risk of harm

The Precautionary Principle

Table 2 Pros and cons of different regulatory approaches for e-cigarettes (e-cigs)

Regulatory approach	Pros	Cons
Ban on sales	Avoid use by nonintended population	Prevent smokers from using an alternative less harmful product
Ban on nicotine-containing products	Avoid nicotine intake by nonintended population	Does not address risk of using nonnicotine liquids; ban on nicotine will make smoking cessation extremely difficult
Medicinal regulation	Ensure maximum safety	Extremely expensive; will make products unattractive; will hinder innovation
Tobacco regulation	Ensure the application of restrictions similar to tobacco products	No need for applying restrictions similar to tobacco products; false impression that e-cigs are of equal risk to tobacco products; will discourage use by smokers
Consumer regulation	E-cigs are used as consumer products	Does not address specific issues relevant to e-cigs like nicotine content; may create the impression that they could be used by the whole population as a new habit

The Washington Post
Democracy Dies in Darkness

Speaking of Science

New report finds no evidence that having sex with robots is healthy

By Ben Guarino June 4 Email the author

New research says there is no evidence that intimacy with a robot is healthy, according to a report in the BMJ Sexual & Reproductive Health journal June 4.
(Allie Caren/The Washington Post)

Precautionary Principle Hard At Work

Chantal Cox-George, a doctor at St. George's University Hospitals in Britain, and Susan Bewley, an obstetrician at King's College London, scoured the medical literature for reports concerning the health aspects of sex robots. They finished their search as they began: empty-handed.

No primary research data on sex robots exists, the doctors concluded. "We advise that sexbots shouldn't be used in medical practice," Cox-George said, "at least not unless that forms part of robust and ethical research."

For the time being, and given the lack of data, Cox-George and Bewley conclude that medical professionals should apply what is known as the precautionary principle: "There is a social responsibility to protect the public from harm, unless findings emerge to show no harm," Cox-George said. In the absence of evidence, in other words, clinicians should steer patients away.

PUBLIC HEALTH STANDARD

In general, FDA shall issue an order under section 911(g)(1) of the FD&C Act (risk modification order) only if it determines the applicant has demonstrated that the product, as it is actually used by consumers, will:

- Significantly reduce harm and the risk of tobacco-related disease to individual tobacco users; and
- Benefit the health of the population as a whole taking into account both users of tobacco products and persons who do not currently use tobacco products.

Tobacco Science Wars

Stalemate; Both sides; Cherry picking

Industry Science (MRTP, PMTA applications)

FDA Science (e.g., PATH, CDC labs; reduced nicotine studies, modeling)

“Independent” science (TCORS?, NIH?, Foundations?)

Other

Safety studies (reduced risk v. cigs)

Surveillance studies (pre- and post-market)

- **Youth samples?**
- **PATH Study (other national studies)**

Modeling studies

Switching studies (dual use concerns-conversion)

Communication studies (messages, intentions)

MRTP Guidance