e-Journal of Cardiology Practice
Current Volume
Previous volumes - e-Journal of Cardiology Practice
e-Journal of Cardiology Practice - Articles by Theme
Subscribe

New tobacco product regulations in the era of reduced harm. Should Europe follow the FDA's example?

Vol. 19, N° 10 - 20 Jan 2021

Dr. Dimitri Richter

Since the time of Hippocrates medicine has had as a principle "First do not harm"; however, today we find ourselves facing a modern-day dilemma.

In current smokers who systematically fail to quit, do we propose alternative smoking products offering a reduced exposure to harmful chemicals? We are facing the dilemma as to whether we should propose a less harmful product for a deadly habit or whether we should insist only on smoking cessation and leave the smokers to decide for themselves. How can an average clinician judge how less harmful a product is? Which regulatory agency will decide on this crucial matter?

Topic(s): *Risk Factors and Prevention;*

Introduction

In 2019, according to the Centers for Disease Control and Prevention (CDC), current smoking in the USA had declined from 20.9% in 2005 to 14.0%, and the proportion of "ever smokers" who had quit had increased [1].

According to the World Health Organization (WHO) European Region, Europe has the highest prevalence of tobacco smoking among adults (28%) and amongst the highest prevalence of tobacco use by adolescents, leading to one of the highest proportions of deaths attributable to tobacco use. The WHO has estimated that tobacco use is currently responsible for 16% of all deaths in adults over 30 in the European Region, with many of these deaths occurring prematurely. This is in contrast to the African or the Eastern Mediterranean Regions, which have rates of tobacco-attributable deaths of 3% and 7%, respectively, with the global average being 12%.

The gap in smoking prevalence between male and female adults is now very small (<5%) in countries such as Denmark, Ireland, the Netherlands, Norway, Sweden and the United Kingdom [2].

Although the majority of smokers are aware that smoking will decrease their life expectancy by 10 years on average, they still find it difficult to stop smoking: 73% of smokers wish to stop; 22% try and less than 5% succeed without assistance. Structured help with smoking cessation improves the chances of success of attempts to quit [3].

In this global environment, the scientific community faced a huge moral dilemma. Taking into account that, since the time of Hippocrates, medicine has had as a principle "First do not harm", today we find ourselves facing a new dilemma.

In current smokers who systematically fail to quit, but whose health condition makes smoke harm reduction mandatory, do we propose alternative smoking products which offer a reduced but existing exposure to harmful chemicals? We are facing the dilemma as to whether we should propose a less harmful product for a deadly habit or whether we should insist only on smoking cessation and leave the smokers to decide by themselves. How can an average clinician judge how less harmful a product is? Which regulatory agency should decide on this crucial matter?

We have a lack of guidance in Europe on such a sensitive public health matter. Examining the FDA's example could possibly help us improve our actual regulatory standing on this important public health matter.

Tobacco products - reduced harm and the FDA

The Federal Food, Drug, and Cosmetic Act (FD&C Act), as modified by the Family Smoking Prevention and Tobacco Control Act (Tobacco Control Act) in 2009, gives the Food and Drug Administration (FDA) a powerful tool to improve public health by ensuring that new tobacco products are reviewed prior to being introduced onto the market and that tobacco products marketed with claims of reduced exposure, harm or risk of tobacco-related disease actually do reduce exposure or harm or can reduce the risk of disease [4].

New tobacco products must be reviewed and issued a marketing order by the FDA prior to being marketed to consumers [5]. Tobacco products that intend to be marketed with claims of reduced exposure to the harmful substances in tobacco smoke or claims of reduced risk of causing tobacco-related disease have to prove that they reduce exposure or risk of disease. Such new or modified risk tobacco products (MRTPs) must benefit not only individual smokers, but also the health of the population as a whole [6].

The Modified Risk Tobacco Product (MRTP) provisions

"The Modified Risk Tobacco Product (MRTP) provisions may be valuable tools in the effort to promote public health by reducing the morbidity and mortality associated with tobacco use. Particularly, if companies take advantage of these provisions by making bold, innovative product changes, it can enable a significant reduction or elimination, of the toxicity or addictiveness of tobacco products, or even both" [6].

The FDA review of the MRTP applications aims to ensure that marketing and claims about the risks of tobacco products are substantiated and supported by scientific evidence, and that the advertising and labelling of these products are truthful and not misleading so that consumers understand the claims correctly.

To ensure the promotion of public health, the FDA also considers the potential impacts, such as the likelihood that users who would otherwise have quit tobacco use will instead switch to the MRTPs or use MRTPs along with other tobacco products, or the likelihood that non-users of tobacco products will start using an MRTP [6]. MRTP applications have to be available for public comment before the FDA takes action.

The FDA must also refer MRTP applications to the Tobacco Products Scientific Advisory Committee (TPSAC), which consists of experts in safety, dependence and health issues related to tobacco products and non-voting members of the industry. The TPSAC provides advice and recommendations to the FDA and, while those recommendations are not binding, the FDA considers them along with other relevant information - including public comments - when making a final decision.

The FDA can issue an order authorising the marketing of an MRTP only if the evidence submitted in the application meets the requirements of Section 911 of the FD&C Act. The FDA's objective is to complete the review of MRTP applications within 360 days of receipt, but this is not a statutory requirement [6].

An FDA order permitting the marketing of an MRTP is not permanent; it is for a fixed period of time. To continue to market an MRTP after the set term, a company must seek renewal of the order and the FDA must determine that actual experience in the marketplace confirms the scientific findings contained in the application.

In addition, companies will be required to conduct post-market surveillance and studies and submit the results to the FDA annually. The FDA will review these results and collect further information about the product's use and related health risks. If, at any time, the FDA determines that it can no longer make the determinations required for an MRTP order, the FDA has authority to withdraw the order, thereby extinguishing the authority for the manufacturer to make any reduced exposure or reduced risk claims for the product.

Given the breadth of evidence needed to support the issuance of an MRTP order, it is unlikely that a single study will provide sufficient evidence to support the FDA's issuance of an order. Furthermore, it is unlikely that a set of studies of one type will provide sufficient evidence to support the issuance of an order. Therefore, the FDA recommends that companies provide information from a number of studies of different types in order to address the full range of areas of investigation so that the FDA can determine whether or not it can issue an order for the MRTP. These include product analyses, non-clinical studies, studies in adult human subjects, and secondary data analyses and modelling [7].

Product analyses

Product analyses regarding the chemistry and engineering of the product may be used to verify and validate the information submitted regarding the formulation of the product. In addition, product analyses will facilitate the FDA's understanding of the product, the potential for exposure to harmful or potentially harmful constituents from use of the product, and provide context for evaluating other data submitted in an MRTP application. For each product, the FDA recommends that applicants conduct product analyses to determine levels of harmful and potentially harmful constituents (HPHC), including smoke constituents, as appropriate to the product [7].

Non-clinical studies

Non-clinical studies include in vitro, in vivo, and ex vivo studies. The results of these studies may offer useful information about the health risks and abuse liability of a tobacco product. These studies may also provide context for data obtained from other types of studies, such as product analyses and human studies.

The FDA recommends that applicants conduct non-clinical studies to address the known clinical toxicities of tobacco products and evaluate a range of potential toxicities of the product compared to other tobacco products on the market. Applicants should choose appropriate models for non-clinical studies that are sufficiently sensitive for the evaluation of the selected endpoint and be able to provide support for the model used, including an explanation of the sensitivity and probative value of the model chosen. For in vivo animal studies, researchers should administer the test product to animals by a route representative of human exposure, where feasible [7].

Studies in adult human subjects

Studies in human subjects include clinical investigations, epidemiological studies, consumer perception studies, actual use studies and other studies that involve humans consuming or interacting with the product, its proposed labelling and/or marketing materials. Human studies provide the FDA with information critical for determining what effect the product may have on the health of individuals and on the population as a whole if the product is commercially marketed as an MRTP [7].

Secondary data analyses and computational modelling

The FDA acknowledges the difficulties inherent in making pre-market assessments of the effect that the introduction of a modified risk product would have on the population as a whole and the public health. The FDA encourages the development and application of innovative analytical methods to make preliminary estimates of the potential effects of some change in the marketplace [7].

Finally, applicants should conduct well-designed studies and analyse and provide sufficient information about those studies and analyses to allow critical evaluation and so that other investigators could conduct similar studies and analyses to replicate the applicant's findings. This will help to provide adequate assurance that a finding in a study can be replicated to show that the finding is not the result of unanticipated, undetected, or systematic biases, study site or investigator-specific factors, or chance. It will also provide a safeguard against instances in which the results of a study are the product of fraudulent reporting of scientific studies because it allows verification of study results [7].

IQOS MRTP order [8,9]

In 2020 the FDA authorised the "IQOS Tobacco Heating System" as a modified risk tobacco product (MRTP). This marks the second product ever to be authorised as an MRTP (the first one was snus, which was also the first tobacco product to receive an "exposure modification" order), and permits marketing with the following information:

- The IQOS system heats tobacco but does not burn it.
- This significantly reduces the production of harmful and potentially harmful chemicals.
- Scientific studies have shown that switching completely from conventional cigarettes to the IQOS system significantly reduces your body's exposure to harmful or potentially harmful chemicals.

According to the FDA's Mitch Zeller, J.D., director of the FDA's Centre for Tobacco Products, about this decision, "Through the MRTP application process, the FDA aims to ensure that information directed at consumers about reduced risk or reduced exposure from using a tobacco product is supported by scientific evidence. Data submitted by the company shows that marketing these particular products with the authorised information could help addicted adult smokers' transition away from combusted cigarettes and reduce their exposure to harmful chemicals, but only if they completely switch.

The FDA will closely monitor how IQOS is used by consumers to determine if these products meet this potential and do not cause increased use among youth. It is important to note that these products are not safe, so people, especially young people, who do not currently use tobacco products should not start using them or any other tobacco product".

Post-market surveillance and studies to determine the impact of this order on consumer perception, behaviour and health and close monitoring of youth awareness and use of the products are required to enable the FDA to review the accuracy of the determinations and to ensure that the marketing of MRTPs does not have unintended consequences for youth use.

The company had also requested a risk modification order, but the FDA determined that the evidence had not demonstrated that the product would significantly reduce harm and the risk of tobacco–related disease to individual tobacco users and benefit the health of the population as a whole. Although reduced risk has not been demonstrated, the totality of evidence presented suggests that a measurable and substantial reduction in morbidity or mortality among individual tobacco users is reasonably likely in subsequent studies.

Despite the concerns that some unknowns may pose, the FDA concluded that the available scientific evidence demonstrates that the issuance of exposure modification orders for IQOS would be appropriate to promote the public health and is expected to 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.

As far as scientific studies are concerned for an MRTP, cancer risk is much easier to study and evaluate than coronary artery disease risk. Measuring known carcinogens quantitatively and qualitatively between IQOS and cigarettes showed a consistent reduction of known carcinogens of about 90% in IQOS. However, as far as coronary artery disease is concerned, the evaluation is much more complicated. We do not have a single substance that increases cardiovascular risk and nicotine is not the cause of atherosclerosis. We have pulse wave velocity studies, aortic stiffness studies, and biochemical indices studies, with the majority of them demonstrating reduced harm in relation to cigarette smoking. However, due to the short period of IQOS presence in the market, there are no epidemiological studies to prove a decrease in cardiovascular disease [10-12].

The snus paradox [13]

Snus - a moist powder smokeless tobacco product that is placed inside the lip, between the lip and gums, for extended periods - was the first tobacco product to be authorised by the FDA as an MRTP in 2019. It could be marketed with the claim "Using General Snus instead of cigarettes puts you at a lower risk of mouth cancer, heart disease, lung cancer, stroke, emphysema, and chronic bronchitis". So far, it is the only product to be permitted such a claim (the highest possible health claim). The FDA made this authorisation after reviewing scientific evidence submitted by the company that supports this claim. The fact that this product has a long-standing tradition in Sweden helped by providing epidemiological studies confirming this long-term safety claim [14].

In an effort to help prevent youth access and exposure, the agency has also placed stringent advertising and promotion restrictions on the product, including a requirement to restrict advertising to adults.

Since 1992, the sale of snus is expressly prohibited in most EU countries, with only Sweden, and Norway and recently Switzerland (not EU countries), receiving an exemption. This is one of the most paradoxical cases where the EU authorities allow the sale of conventional cigarettes and prohibit the sale of an alternative tobacco product where scientific evidence, including long-term epidemiological studies, shows a lower risk of cancer, heart disease and chronic bronchitis.

According to the University of Bath, this prohibition was a response to aggressive attempts to introduce US-style smokeless tobacco (Skoal Bandits) into Europe. The U.S. Smokeless Tobacco Company (UST), co-founder of the European lobby group ESTOC, marketed the product in several European countries, including the UK and Ireland. A peer-reviewed study from the University of Bath, analysing internal tobacco industry documents, demonstrated that tobacco companies saw smokeless tobacco as having the potential "to generate new profits without cannibalising existing profits from cigarettes" in Europe, and that young people were a key target. Skoal Bandits was advertised as "the new way to enjoy tobacco". In the UK, students were both the target and the means of promotion.

An 1985 internal BAT memo reported that UST was "working the Universities", including paying students to promote Skoal Bandits to peers. Due to fear of this new tobacco product spreading across Europe, and the aggressive marketing tactics to young people, the European Parliament called for a total EU-wide ban on "oral tobacco" sales in September 1987. This call was preceded by a recommendation from the WHO urging countries with no history of smokeless tobacco use to ban this type of tobacco pre-emptively, in order to prevent a future public health problem. In 1992 an EU-wide sales ban of oral tobacco was enacted under the amended Labelling Directive. This prohibition was reaffirmed in 2001, and again in 2014 [15].

Summary of the regulatory status of e-cigarettes in the USA [16]

After years of no regulation, in May 2016 the FDA extended the law for New Tobacco Products to e-cigarettes for the first time. The producers of e-cigarettes will be required to register with the FDA and provide a detailed account of their products' ingredients as well as their manufacturing processes. Producers will have to apply to the FDA for permission to sell their products, will be subject to FDA inspections and will not be allowed to market their products as light or mild without agency approval. In practice, this means that any e-cigarette that is currently on the market has to have a pre-market application filed with the FDA by 9 September 2020; otherwise it is marketed illegally. The deadline to submit applications was actually decided by a court after the FDA was sued by public health groups for delay. Eventually, the court set a date as the due date, which everyone accepted. The appearance of EVALI (E-cigarette or Vaping Use-Associated Lung Injury) disease in e-cigarette smokers probably acted as an accelerator timewise [17].

Essentially, the FDA will now be authorising the products that are currently on the market retroactively. To date, the FDA has not authorised any e-cigarettes as "appropriate for the protection of public health".

Finally, in 2020 the FDA issued guidance that essentially bans any flavoured, cartridge-based e-cigarettes, other than tobacco- or menthol-flavoured ones; e-cigarettes for which the manufacturer has failed to take adequate measures to prevent minors' access; and any e-cigarettes that are targeted to minors or likely to promote use by minors. To make matters even more complicated, some states and localities have also taken action to ban flavoured e-cigarettes.

Conclusion

Is this the ideal way to proceed? Difficult to say. However, the existence of a regulatory evaluating mechanism on new tobacco products and the institutional scientific evaluation of MRTPs seems to be the way forward. Europe should probably follow sooner rather than later. After all, as Mark Twain said, "Giving up smoking is the easiest thing in the world. I know because I've done it thousands of times.".

References

1. Current Cigarette Smoking Among Adults in the United States. Centres for Disease Control and Prevention. (Last accessed 5th January 2021)
2. WHO. Data and statistics. (Last accessed 5th January 2021).
3. Joly B, Perriot J, d'Athis P, Chazard E, Brousse G, Quantin C. Success rates in smoking cessation: Psychological preparation plays a critical role and interacts with other factors such as psychoactive substances. *PLoS One*. 2017;12:e0184800.
4. Centre for Tobacco Products Overview. (Last accessed 5th January 2021).
5. Guidance for Industry: Applications for Premarket Review of New Tobacco Products. *FDA.*
6. Guidance for Industry: Modified Risk Tobacco Products Applications. *FDA*.
7. Guidance for Industry. Modified Risk Tobacco Product Applications / DRAFT GUIDANCE. *FDA.*
8. FDA NEWS RELEASE. FDA Authorizes Marketing of IQOS Tobacco Heating System with 'Reduced Exposure' Information.
9. FDA U.S. Food & Drug Administration. Scientific Review of Modified Risk Product Application (MRTPA) Under Section of 911(d) of the FD&C Act – Technical Project Lead.
10. Biondi-Zoccai G, Sciarretta S, Bullen C, Nocella C, Violi F, Loffredo L, Pignatelli P, Perri L, Peruzzi M, Marullo AGM, De Falco E, Chimenti I, Cammisotto V, Valenti V, Coluzzi F, Cavarretta E, Carrizzo A, Prati F, Carnevale R, Frati G. Acute Effects of Heat-Not-Burn, Electronic Vaping, and Traditional Tobacco Combustion Cigarettes: The Sapienza University of Rome- Vascular Assessment of Proatherosclerotic Effects of Smoking (SURVAPES) 2 Randomized Trial. *J Am Heart Assoc*. 2019;8:e010455.
11. Lüdicke F, Ansari SM, Lama N, Blanc N, Bosilkovska M, Donelli A, Picavet P, Baker G, Haziza C, Peitsch M, Weitkunat R. Effects of Switching to a Heat-Not-Burn Tobacco Product on Biologically Relevant Biomarkers to Assess a Candidate Modified Risk Tobacco Product: A Randomized Trial. *Cancer Epidemiol Biomarkers Prev.* 2019;28:1934-43.
12. Ratajczak A, Jankowski P, Strus P, Feleszko W. Heat Not Burn Tobacco Product—A New Global Trend: Impact of Heat-Not-Burn Tobacco Products on Public Health, a Systematic Review. *Int J Environ Res Public Health.* 2020;17:409.
13. FDA NEWS RELEASE. FDA grants first-ever modified risk orders to eight smokeless tobacco products.
14. Lee PN. Summary of the epidemiological evidence relating snus to health. *Regul Toxicol Pharmacol.* 2011;59:197-214.
15. University of Bath. Snus: EU Ban on Snus Sales. Tobacco Tactics. (Last accessed 5th January 2021)
16. Federal Register. DEPARTMENT OF HEALTH AND HUMAN SERVICES - Deeming Tobacco Products To Be Subject to the Federal Food, Drug, and Cosmetic Act. [FR Doc. 2016-10685 Filed: 5/5/2016 8:45 am; Publication Date: 5/10/2016]
17. E-Cigarettes and Vaping-Related Disease.

Notes to editor

Author:

Dimitris J. Richter, MD, FESC, FAHA

Head of Cardiac Department, Athens Euroclinic, Athens, Greece

Address for correspondence:

Dr Dimitris J. Richter

Alkmanos 33, 11528, Athens, Greece

E-mail: richterdimitri@hotmail.com

Author disclosures:

The author has received travel grants, lecture and advisory board fees from Amgen, Sanofi, Bayer, Boehringer, MSD, Astra, Leo, Teva, Mylan, Menarini, Servier, AstraZeneca, Vianex and Elpen.

The content of this article reflects the personal opinion of the author/s and is not necessarily the official position of the European Society of Cardiology.