How Would an Ethically Responsible FDA Evaluate PMTA and MRTP Applications and Issue Related Orders?

ERIC N. LINDBLOM*

ABSTRACT

Pursuant to the U.S. Tobacco Control Act, any tobacco product that was not already legally on the U.S. market on February 15, 2007 or is not substantially equivalent to a product that was on the market on that date may not enter or stay on the market unless it has submitted a Premarket Tobacco Product Application (PMTA) to the U.S. Food and Drug Administration (FDA) and received a permissive PMTA order finding that it is "appropriate for the protection of the public health" (AFPPH) to allow the product's marketing pursuant to the terms of that order.

So far, FDA has not been actively enforcing this requirement, and all e-cigarettes and some cigars and other tobacco products currently on the U.S. market are illegal because they do not have a permissive PMTA order. But a federal court has ordered FDA to take enforcement action against those illegal tobacco products unless their manufacturer or importer submits an application to secure a permissive PMTA order by September 9, 2020. In addition, FDA has announced that it will pull off the market all cartridge-based e-cigarettes with flavors other than tobacco or menthol and allow them to be marketed only if they first secure a permissive PMTA order.

Accordingly, FDA must evaluate numerous new PMTAs for e-cigarettes and other tobacco products, decide whether to allow their marketing and, when allowed, determine what product, labeling, and marketing requirements and restrictions to include in the permissive PMTA orders to ensure that the product's marketing will be AFPPH. While the core meaning of the AFPPH standard is clear (to benefit the health of the population as a whole), the statute and other applicable law provide FDA with considerable discretion to determine exactly how to interpret and apply the standard in specific situations when the potential harms and benefits from allowing the marketing of a product cannot be determined with any precision or certainty.

So far, FDA has issued only a few permissive PMTA orders (for some snus, heat-not-burn, and reduced-nicotine-cigarette products). Neither those orders nor any other FDA public documents have clarified how FDA will be exercising its discretion to interpret or apply the AFPPH standard in the PMTA (or any other) context. Nor has FDA explained how it will be evaluating PMTAs and structuring any permissive orders given the inevitable uncertainties when trying to determine the extent to which

* Eric N. Lindblom is a legal and policy consultant on tobacco control and cannabis legalization matters and a Senior Scholar at Georgetown Law's O'Neill Institute for National & Global Health Law. He was Director of the Office of Policy at FDA's Center for Tobacco Products from 2011 to 2014 and previously served as General Counsel and Director for Policy Research at the Campaign for Tobacco-Free Kids. The development of this Article was supported by a Greenwall Foundation "Making a Difference in Real-World Bioethics Dilemmas" grant.

the marketing of a tobacco product might benefit or harm the public health or produce other health or non-health benefits, harms, or risks.

This paper considers how FDA could interpret and apply the AFPPH standard and otherwise evaluate PMTAs and structure any related permissive orders to make the agency's final decisions and orders not only AFPPH but also as ethically appropriate and beneficial as possible. To do that, the paper looks carefully at what applicable law says FDA must, may, and cannot do when evaluating applications and structuring new product orders, and then considers how FDA could most ethically exercise its legal powers and discretion in this context pursuant to the major applicable ethical perspectives of utilitarianism, bioethics, and public health ethics. It also applies this same process to consider how FDA might issue the most appropriate and ethical modified risk tobacco product (MRTP) orders that manufacturers and importers must obtain before labeling or marketing any tobacco products with any explicit or implicit reduced-risk or reduce-exposure claims. To expand and refine its analysis, the paper then considers how FDA might most appropriately and ethically evaluate applications for PMTA or MRTP orders for e-cigarettes and what specific product, labeling, and marketing requirements and restrictions available research, experience, and analysis indicates FDA should include in any related permissive orders to make them both AFPPH and otherwise as ethically appropriate as possible.

INTRODUCTION

Smoking and other tobacco use in the United States still causes close to half a million deaths each year, while more than 16 million Americans suffer from tobacco-caused disability and disease.[1] To try to prevent these tobacco use harms from getting worse, and perhaps help to reduce them, the Tobacco Control Act (TCA) prohibits any brand new tobacco product types or variants from entering the market unless the manufacturer first submits a Pre-Market Tobacco Application (PMTA) to FDA and obtains an order from the agency finding that allowing the product's marketing would be "appropriate for the protection of the public health."[2] Similarly, the Act prohibits any tobacco product from being marketed with reduced-risk or reduce-exposure claims unless the manufacturer first submits a Modified Risk Tobacco Product (MRTP) application and receives an order from FDA finding that allowing the claim is not only accurate and not misleading but will also "benefit the health of the population as a whole" (which is defined to be virtually identical to the "appropriate for the protection of the public health" standard).[3]

Although it might be difficult to imagine that allowing the marketing of a tobacco product could be "appropriate for the protection of the public health" (AFPPH), a PMTA or MRTP order could produce public health gains by prompting users of more harmful tobacco products (who would not otherwise quit all use) to switch to the less-

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[1] *See, e.g.*, Maddy Bolger, *Toll of Tobacco in the United States of America*, CAMPAIGN FOR TOBACCO-FREE KIDS (Jan. 13, 2020), https://www.tobaccofreekids.org/assets/factsheets/0072.pdf [https://perma.cc/AC4M-8LWZ].

[2] Family Smoking Prevention and Tobacco Control Act (TCA) § 910, 21 U.S.C. § 387j (2018).

[3] TCA § 911, 21 U.S.C. § 387k (2018). The core public health standard for issuing PMTA and MRTP orders are virtually identical, except the MRTP standard does not always use the words "appropriate for the protection of the public health." For simplicity's sake, they will both be referred to as the "appropriate for the protection of the public health" (AFPPH) standard. *Compare* TCA § 910(c)(4), 21 U.S.C. § 387k(c)(4) (2018), *with* TCA § 911(g)(1) & (2)(A), 21 U.S.C. § 387j (g)(1) & (2)(A) (2018).

harmful MRTP or PMTA products or by prompting youth who would otherwise initiate into more harmful tobacco use to use the less-harmful products instead.[4]

To date, FDA has issued PMTA orders to allow three new types of tobacco product on to the U.S. market—eight Swedish Match smokeless tobacco snus products, four Philip Morris IQOS inhalable "heat not burn" products, and two 22nd Century Group reduced-nicotine cigarettes—and FDA subsequently issued MRTP orders to allow the snus and IQOS products to be marketed with, respectively, reduced-risk and reduced-exposure claims compared to smoking.[5] But FDA's evaluations of the applications did not identify all of the different ways allowing the products on the market or allowing the relative-risk claim might prompt new harm-increasing behaviors by youths and adults. Although FDA acknowledged that each of the orders could end up producing a negative net impact on the public health, FDA did not attempt to compare the likelihood and size of those possible negative results against the likelihood and size of the desired public health gains from the orders. Consequently, FDA could not determine that issuing each of the orders would produce a greater chance of producing a net public health gain than producing a net harm to the public health. In addition, the final PMTA and MRTP orders failed to include readily available restrictions and requirements on the products and their marketing that would have reduced the risk of producing a negative net public health impact or reduced unnecessary new individual or subpopulation health harms or risks caused by the order. These failures directly call into question whether the orders were actually AFPPH, as FDA concluded (under any possible clarification of that standard).[6]

This paper considers how FDA could, consistent with the TCA and other applicable law, most ethically and effectively clarify the remaining gray areas of the AFPPH standard, evaluate PMTA and MRTP applications, and then structure any related permissive orders to ensure they are not only AFPPH and otherwise legally viable but also as ethically appropriate as possible within applicable legal, practical, and analytical constraints. To be most helpful and relevant, the paper's ethical analysis will apply those ethical perspectives most frequently used to evaluate, guide, or critique

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[4] For example, issuing permissive PMTA or MRTP orders for e-cigarettes found to be less harmful than cigarettes could secure health gains by increasing smoker switching and shifting youth initiation from smoking to e-cigarette use. But the order might also increase health harms by prompting some smokers to engage in dual use instead of quitting all smoking or all tobacco-nicotine use or to switch completely to using only e-cigarettes instead of quitting all use; by reducing cessation among e-cigarette users; by increasing relapse to e-cigarette use among former smokers who would not otherwise relapse; and by prompting initiation among those who would otherwise not use any tobacco-nicotine product. *See generally, e.g.*, Sara Kalkhoran & Stanton A. Glantz, *Modeling the Health Effects of Expanding E-Cigarette Sales in the United States and United Kingdom: A Monte Carlo Analysis*, 175 JAMA INTERNAL MED. 1671 (2015).

[5] *See Premarket Tobacco Marketing Orders*, FOOD & DRUG ADMIN., https://www.fda.gov/tobacco-products/premarket-tobacco-product-applications/premarket-tobacco-product-marketing-orders [https://perma.cc/2FVG-JDBX] (last updated Jan. 21, 2020) [hereinafter Premarket Tobacco Product Marketing Orders]; *Modified Risk Orders*, FOOD & DRUG ADMIN. (Oct. 22, 2019), https://www.fda.gov/tobacco-products/advertising-and-promotion/modified-risk-orders [https://perma.cc/4457-DWUL] [hereinafter Modified Risk Orders].

[6] *See* Eric N. Lindblom, *The Tobacco Control Act's PMTA & MRTP Provisions Mean to Protect the U.S. From Any New Tobacco Products That Will Not Reduce Health Harms—But FDA Isn't Cooperating*, 23: 2 J. HEALTH CARE L. & POL'Y (forthcoming 2020) (manuscript), https://oneill.law.georgetown.edu/wp-content/uploads/Comments-Draft-Lindblom-FDA-PMTA-Article-10-24-19.pdf [https://perma.cc/759V-XLS4] (providing a detailed analysis of the legal failings of FDA's PMTA and MRTP orders for the Swedish Match Snus and Philip Morris IQOS products).

public health policymaking: utilitarianism,[7] bioethics (with its four core principles of beneficence, nonmaleficence, justice, and respecting personal autonomy),[8] and public health ethics.[9] By definition, this analysis will necessarily include consideration of the ethical goal of reducing inequitable health disparities, the "harm principle,"[10] and the related frequent claims by libertarians and the tobacco industry that personal autonomy (or smoker's rights) should be given predominant consideration.[11]

Reaching any clear conclusions for policy making through ethical analysis can be difficult given that different ethical perspectives often conflict with each other or have conflicting goals, themselves.[12] In the context of public health and tobacco control

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[7] Generally, seeking "the greatest good [or happiness] for the greatest number." *E.g.*, Afschin Gandjour & Karl W. Lauterbach, *Utilitarian Theories Reconsidered: Common Misconceptions, More Recent Developments, and Health Policy Implications*, 11 HEALTH CARE ANALYSIS 229, 231–32 (2003); *see also* OLIVIER BELLEFLEUR & MICHAEL KEELING, UTILITARIANISM IN PUBLIC HEALTH (2016), http://www.ncchpp.ca/127/Publications.ccnpps?id_article=1527 [https://perma.cc/45H9-P592].

[8] *See, e.g.*, TOM L. BEAUCHAMP & JAMES F. CHILDRESS, PRINCIPLES OF BIOMEDICAL ETHICS (7th ed. 2013); Thomas R. McCormick, *Principles of Bioethics*, UW MED., https://depts.washington.edu/bhdept/ethics-medicine/bioethics-topics/articles/principles-bioethics [https://perma.cc/3QSL-TKY6] (providing descriptions of bioethics in its original context of medical patient care); *see also* Peter Schroeder Bach et al., *Teaching Seven Principles for Public Health Ethics: Towards a Curriculum for a Short Course on Ethics in Public Health Programmes*, 15 BMC MED. ETHICS 73 (2014), https://pubmed.ncbi.nlm.nih.gov/25288039/ [https://perma.cc/4Y27-ZH6G] (applying bioethics to public health and to tobacco control policymaking and adding health maximization, efficiency, and proportionality to the four core principles); Brian J. Fox, *Framing Tobacco Control Efforts Within an Ethical Context*, 14 TOBACCO CONTROL ii38 (Suppl. II 2005) (adding two procedural principles: transparency and truthfulness). The principles of bioethics also apply directly to protecting human subjects in FDA and FDA-funded research. HHS Protection of Human Subjects Rule, 45 C.F.R. 46.111(a)(1)–(5) (2019); NAT'L COMM'N FOR THE PROT. OF HUMAN SUBJECTS OF BIOMEDICAL AND BEHAVIORAL RESEARCH, DEP'T OF HEALTH, EDUC., & WELFARE, THE BELMONT REPORT: ETHICAL PRINCIPLES AND GUIDELINES FOR THE PROTECTION OF HUMAN SUBJECTS OF RESEARCH (1979).

[9] Public health ethics focuses on the need to improve the public health, ideally while also reducing inequitable health disparities and otherwise promoting justice, followed by a concern for respecting personal autonomy to the extent possible and reasonable in this public health context. *See, e.g.*, Ruth Faden & Sirine Shebaya, *Public Health Ethics* in THE STANFORD ENCYCLOPEDIA OF PHILOSOPHY (Edward N. Zalta ed., 2016); *see also* Ronald Bayer & Amy L. Fairchild, *The Genesis of Public Health Ethics*, 18 BIOETHICS 473 (2004), https://plato.stanford.edu/archives/win2016/entries/publichealth-ethics/ [https://perma.cc/7W56-29B9]; James F. Childress et al., *Public Health Ethics: Mapping the Terrain*, 30 J.L., MED., & ETHICS 170 (2002); *Public Health Ethics*, CTRS. FOR DISEASE CONTROL & PREVENTION (CDC), https://www.cdc.gov/os/integrity/phethics/index.htm [https://perma.cc/995L-M73L]; PUB. HEALTH LEADERSHIP SOC'Y, PRINCIPLES OF THE ETHICAL PRACTICE OF PUBLIC HEALTH, VERSION 2.2 (2002); *Am. Pub. Health Ass'n*, PUBLIC HEALTH CODE ETHICS (2019), https://www.apha.org/-/media/files/pdf/membergroups/ethics/code_of_ethics.ashx [https://perma.cc/F7ZZ-6F2K]; James Wilson, *Why It's Time to Stop Worrying About Paternalism in Health Policy*, 4 PUB. HEALTH ETHICS 269 (2011).

[10] "[T]he only purpose for which power can be rightfully exercised over any member of a civilized society, against his (sic) will, is to prevent harm to others." John S. Mill, ON LIBERTY 16 (1869); *see also* Larry O. Gostin & Kieran G. Gostin, *A Broader Liberty: J.S. Mill, Paternalism and the Public's Health*, 123 PUB. HEALTH 214 (2009).

[11] *See, e.g.*, Jessica Flanigan, *Public Bioethics*, 6 PUB. HEALTH ETHICS 170 (2013); James E. Katz, *Individual Rights Advocacy in Tobacco Control Policies: An Assessment and Recommendation,* 14 TOBACCO CONTROL ii31 (Supp. II 2005); Elizabeth A. Smith & Ruth E. Malone, *'We Will Speak as the Smoker': The Tobacco Industry's Smokers' Rights Groups*, 17 EUR. J. PUB. HEALTH 306 (2007); *About NATO*, NAT'L ASS'N TOBACCO OUTLETS, http://www.natocentral.org/about [https://perma.cc/2PWV-C46S].

[12] Most fundamentally, choosing to use the ethical perspectives of utilitarianism, bioethics, and public health ethics reduces but does not eliminate the core problems and complications caused for ethical analysis by the subjectivity of moral or ethical values, or the subjectivity of what constitutes the "good" or

policy making, a frequent conflict arises when promoting the ethical goal of improving the overall health of the population contradicts or infringes on such ethical goals as respecting personal autonomy; not causing brand-new health or other harms, especially to already vulnerable or disadvantaged groups; or not increasing inequitable health or other disparities between advantaged and disadvantaged groups. These conflicts arise most clearly and directly when applying a bioethics perspective, with its explicitly articulated and often conflicting core principles of beneficence, non-malfeasance, justice, and autonomy.[13] Although public health ethics generally prioritizes broadly beneficial public health gains over reducing inequitable health disparities, with protecting personal autonomy a less-important third priority, conflicts can still arise when measures to secure overall public health gains leave already disadvantaged groups behind or seriously infringe on personal autonomy.[14] With its single goal of maximizing the overall good for the greatest number, utilitarianism can seem more straight forward or mathematical. But ethical conflicts arise there, too, when securing public health gains also produces negative impacts on other non-health factors contributing to the good or when securing the greatest good conflicts with benefiting the greatest number.[15] To further complicate matters, none of the ethical perspectives provide any clear guidance as to how to resolve possible internal conflicts; nor is it clear how to resolve conflicts between different ethical perspectives.[16]

As explained below, these ethical complications and uncertainties are considerably reduced for FDA PMTA and MRTP deliberations because the TCA and its AFPPH standard puts securing net public health gains (by reducing tobacco-related harms) ahead of any other possible goals, including reducing other ethically relevant harms or securing other ethically relevant benefits. With other applicable laws, the AFPPH standard also requires FDA to include any readily available restrictions or requirements in its permissive PMTA or MRTP orders that would make them more

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"happiness" of utilitarianism. *See, e.g.*, J. L. Mackie, *The Subjectivity of Values*, *in* ETHICS: ESSENTIAL READINGS IN MORAL THEORY (George Sher ed., 2012); George C. Freeman III, *Liberalism and the Objectivity of Ethics*, 47 La. L. Rev. 1235 (1986) (reviewing JAMES S. FISHKIN, BEYOND SUBJECTIVE MORALITY: ETHICAL REASONING AND POLITICAL PHILOSOPHY (1984)); Gandjour & Lauterbach, *supra* note 7.

13 BEAUCHAMP & CHILDRESS, *supra* note 8; McCormick, *supra* note 8.

14 *See supra* note 9. Some possible conflicts and complications are avoided, however, by the fact that lower-income and less-educated persons, and other disadvantaged and vulnerable subpopulations, disproportionately smoke and use other tobacco products and suffer disproportionately from tobacco-caused health harms. *See, e.g.*, Jeffrey Drope et al., *Who's Still Smoking? Disparities in Adult Cigarette Smoking Prevalence in the United States*, 68 CANCER J. FOR CLINICIANS 106, 109 (2018). Accordingly, any non-targeted, non-discriminatory tobacco control intervention that secures significant, broad-based public health gains will almost certainly reduce inequitable tobacco-related health disparities. In addition, tobacco control efforts that reduce tobacco-caused death and disability work directly to increase the personal autonomy of those enabled to live longer or with less or no disability.

15 Gandjour & Lauterbach, *supra* note 7, at 231 n. 4, 234–38; BELLEFLEUR & KEELING, s*upra* note 7, at 5–6.

16 *But see* Raanan Gillon, *Defending the Four Principles Approach as a Good Basis for Good Medical Practice and Therefore for Good Medical Ethics*, 41 J. MED. ETHICS 111 (2015); BEAUCHAMP & CHILDRESS, *supra* note 8, at 22–23 (presenting conditions that should be met when choosing to infringe one ethical principle when conflicts between principles arise, including providing good reasons, infringement will promote a moral or ethical goal, no ethically preferable alternative is available; infringement is minimized; negative effects from infringement are minimized; and all affected parties are treated impartially).

certainly AFPPH, even if that also causes other new ethically relevant harms or risks, such as new non-health harms (unless those new ethically relevant harms and risks are so disproportionately large that accepting them to secure the public health gains could not possibly make sense or be considered rational). Conversely, applicable law also requires FDA to take advantage of any readily available measures it could include in the permissive orders that would reduce any new underlying health harms and risks or certain other ethically relevant harms and risks caused by the orders (unless doing so would reduce the likelihood or size of the orders' net public health gains). Nevertheless, numerous ethical and related issues arise when trying to determine how FDA might operate most ethically within this legal framework, especially given the remaining ambiguities in the AFPPH standard and the inevitable difficulties when trying to estimate and compare the different future positive and negative health impacts and other ethical impacts from possible PMTA or MRTP orders.

Accordingly, this paper will show what FDA must, may, and cannot do in the PMTA and MRTP contexts; how FDA could most ethically exercise its discretion to interpret the remaining gray areas in the AFPPH standard in the PMTA and MRTP contexts; and how the agency could then act accordingly in the most ethical fashion when processing PMTA and MRTP applications and issuing any permissive orders. To do that, the paper will describe what an ethically ideal AFPPH standard might look like (under the chosen ethical perspectives) and what ethically ideal PMTA or MRTP orders might look like, and it will consider how FDA could use those ideals to guide its actions. It will then apply that analysis to the hypothetical case of FDA considering PMTA and MRTP applications to allow e-cigarettes to enter or stay on the U.S. market as legal tobacco products and to be advertised and promoted with reduced-risk claims.[17]

Besides providing ethical guidance for how FDA could more constructively and ethically handle PMTA and MRTP applications and its development of related orders, the paper's ethical analysis provides direct insights into how FDA might use its existing authorities to regulate all tobacco products more ethically to protect and promote the public health more effectively. It also offers an ethical framework that the public health community could use when evaluating and commenting on MRTP applications submitted to FDA (which must be made available for public comment), on PMTA applications that FDA chooses to make available for public comment, or on proposed FDA tobacco control rules going through the required notice-and-comment

[17] Currently, all e-cigarettes on the U.S. market are illegal tobacco products because they have not received the permissive PMTA orders from FDA required by the TCA. They have been allowed to stay on the market solely because FDA has chosen not to enforce against them. Pursuant to a U.S. District Court order, FDA may not continue allowing all e-cigarettes to stay on the market illegally and any e-cigarettes that have not submitted an application for a PMTA order by September 9, 2020 are subject to being immediately pulled off the market. *Coronavirus (COVID-19) Update: Court Grants FDA's Request for Extension of Premarket Review Submission Deadline for Certain Tobacco Products Because of Impacts from COVID-19*, FOOD & DRUG ADMIN. (2020), https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-court-grants-fdas-request-extension-premarket-review-submission-deadline [https://perma.cc/9YEG-TVPG]; Am. Acad. of Pediatrics v. FDA, 379 F. Supp. 3d 461 (D. Md. 2019) enforced 399 F. Supp. 3d at 487; appeals rejected or dismissed in In re Cigar Assoc. of Am., 2020 WL 2116554 (4th Cir. May 4, 2020). Although FDA does not publicly disclose all PMTA submissions, at least one PMTA for a major e-cigarette brand has been submitted since the court issued its order and more are bound to be submitted if they have not already. *See, e.g.*, Press Release, *Reynolds American Inc. Submits Premarket Tobacco Product Application for VUSE Products* (Oct. 11, 2019), https://s2.q4cdn.com/129460998/files/doc_news/2019/10/11/PMTA-Release-FINAL-191011.pdf [https://perma.cc/VJ32-RB49].

process. In this way, the paper also provides an ethical framework for evaluating tobacco control proposals or actions at other levels of government in the United States, and in other countries, as well.

I. WHAT DO THE TCA AND OTHER APPLICABLE LAWS SAY FDA MUST, MAY, AND CANNOT DO WHEN ISSUING PMTA/MRTP ORDERS?

FDA must issue responsive PMTA and MRTP orders whenever tobacco product manufacturers or importers submit valid applications seeking to obtain them, with the orders stating whether or not FDA has determined that allowing the product on the market or allowing the product to be marketed with modified-risk claims is AFPPH.[18] In both cases, the AFPPH standard is concerned with reducing only the *health* harms and risks to the population *as a whole*.[19] Consequently, the health impacts on certain individuals or subpopulations from issuing a permissive PMTA or MRTP order are not relevant to FDA AFPPH determinations, except to the extent they contribute to the overall impact on the public health, and non-health impacts (including impacts on personal autonomy) are irrelevant except to the extent they also produce impacts on the public health.[20]

However, the Administrative Procedure Act (APA), as incorporated by the TCA, requires that FDA exercise its tobacco control authorities in ways that are "not arbitrary or capricious [or] an abuse of discretion."[21] In general, that standard is quite permissive, requiring only that agencies follow the established procedures for taking their regulatory actions; explain how its regulatory actions and related agency choices about how to structure them promote the relevant statutory purposes (e.g., to protect the public health); and consider all relevant available information, including contrary evidence and analysis and alternative ways the regulatory action might be structured when making their regulatory decisions. When that is done, the courts may strike down an agency's regulatory decision as "arbitrary or capricious" only if it is irrational, incomprehensible, or clearly wrong.[22]

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[18] TCA § 910, 21 U.S.C. § 387j (PMTA orders); TCA § 911, 21 U.S.C. § 387k (MRTP orders). For FDA PMTA and MRTP orders, the burden of proof is on the tobacco product manufacturer submitting the application—i.e., FDA must determine whether the applicant has demonstrated that issuing a permissive order would be AFPPH. TCA § 910(c)(2), 21 U.S.C. § 387j (c)(2) (2018); TCA § 911(g)(1), (2) & (3)(A), 21 U.S.C. § 387k(g)(1), (2) & (3)(A).

[19] TCA § 906(d)(1) & (3), 21 U.S.C. § 387f(d)(1) & (3) (2018); *see also id.* § 907(a)(3) & (4), 907(c)(2) & (3), 21 U.S.C. 387g(a)(3) & (4), 387g(c)(2) & (3); *id.* § 910(c)(2)(A) & (4) & (5), 910(d)(1)(A), 21 U.S.C. 387j(c)(2)(A) & (4) & (5), (d)(1)(A); *id.* § 911(g)(1), 21 U.S.C. 387k(g)(1).

[20] Eric N. Lindblom, *What Is 'Appropriate for the Protection of the Public Health' Under the U.S. Tobacco Control Act,* 74 FOOD & DRUG L.J. 523, 533–40, 541–49 (2020). The TCA also requires that FDA's evaluation of whether a tobacco control rule or order is AFPPH must be comprehensive, considering the public health consequences of the impacts on both users and nonusers, including the effects of the regulatory action on initiation, cessation, dual or multi-product use, switching among tobacco products, relapse, non-user exposure, etc. *Id.* at 549–50.

[21] 5 U.S.C. § 706(2)(A); 21 U.S.C. § 387l(a) & (b).

[22] *See, e.g.*, FERC v. Elec. Power Supply Ass'n, 136 S. Ct. 760, 782 (2016); *see also* Nat'l Ass'n of Home Builders v. Defs. of Wildlife*,* 551 U.S. 644, 658 (2007); U.S. Dep't of Justice Fed. Bureau of Prisons Fed. Corr. Complex Coleman, Fla. v. Fed. Labor Relations Auth., 737 F.3d 779, 785 (D.C. Cir. 2013);

In particular, courts have also found that agencies would be arbitrary or capricious if they fail to take advantage of readily available ways to structure or revise their regulatory actions to reduce any related costs not necessary to promoting the action's statutory purposes (even when the statute does not mention any concerns about costs).[23] These rulings support a broader FDA duty, before issuing a permissive PMTA or MRTP order, to make any readily available changes, within its scope, that will reduce any other undesirable impacts, comparable to or worse than regulatory costs, without impeding the ability of the rule or order to promote the TCA's core purpose, to reduce health harms and risks to the population as a whole.[24] Given that core purpose, FDA would certainly be arbitrary or capricious if it failed to take advantage of readily available ways to adjust a PMTA or MRTP order that would reduce the likelihood and size of any negative net public health impact it could produce or to reduce any underlying new health harms or risks or increased health inequities the order might cause without reducing the likelihood and size of its desired net public health gains.

In regard to reducing public health harms and risks, the TCA is silent as to whether an FDA tobacco control rule or order could be AFPPH if it were likely to secure a net public health benefit but also created a significant risk of producing a negative net public health impact instead. It is difficult to imagine any not-arbitrary-or-capricious interpretation of the AFPPH standard that would find a rule or order "appropriate" if it created a greater risk of producing a serious negative net public health impact instead of a positive one or if it was only marginally more likely to create a small positive net impact than create a much larger negative net impact. But neither the Act nor the not-arbitrary-or-capricious standard or related case law provides any clear guidance for more difficult scenarios. Accordingly, FDA may develop its own interpretation of how the potential gains and possible risks from a possible tobacco control rule or order should be weighed against each other for making AFPPH determinations—so long as its interpretation is not arbitrary or capricious—but FDA has not yet done so.[25]

Associated Fisheries of Maine, Inc. v. Daley, 127 F.3d 104, 110 (1st Cir. 1997); Lindblom, *supra* note 20, at 563–67.

[23] *See, e.g.*, State of La., ex rel. Guste v. Verity, 853 F.2d 322, 331 (5th Cir. 1988); S. Terminal Corp. v. EPA, 504 F2d 646, 655–56, 676 (1st Cir. 1974). These cases, along with other available case law on regulatory agencies being "not arbitrary or capricious," do not suggest that regulatory agencies must choose to implement those discretionary regulatory actions that will best promote their statutory objectives or that will do so effectively with minimum related costs, but only that, once they exercise their discretion to choose what regulatory action to develop (or are required to take a regulatory action), the regulatory agencies must take advantage of any available revisions to the action, within its scope, that will reduce its related costs without interfering with its ability to achieve the statutory goals.

[24] Lindblom, *supra* note 20, at 568–77. A parallel not-arbitrary-or-capricious analysis suggests that agencies may also have a duty to take advantage of readily available ways to structure their regulatory actions so that they promote their statutory purposes more powerfully and effectively, at least when doing that does not significantly or disproportionately increase costs or any equally or more serious undesirable impacts. But there do not appear to be any cases on point one way or the other. *Id.* at 577–81.

[25] On the courts' deference to agency decisions for how to interpret the gray areas, ambiguities, and gaps in their authorizing statutes that cannot be clarified through the statutes' text or legislative history, see, for example, Util. Air Regulatory Group v. EPA, 573 U.S. 302, 325 (2014); U.S. v. Bean, 537 U.S. 71, 77 (2002); Chevron v. Nat. Res. Def. Council, Inc., 467 U.S. 837, 843–44 (1984). On FDA's failure, to date, to clarify the remaining gray areas of the AFPPH standard, see Lindblom, *supra* note 20, at 526; Lindblom, *supra* note 6 (regarding FDA not clarifying how the AFPPH standard applies in the context or evaluating PMTA and MRTP applications and issuing related orders).

The TCA also provides no guidance as to how FDA is meant to handle the inevitable uncertainties in trying to identify and predict the future health or other relevant impacts from issuing a specific PMTA or MRTP order or order variant when the agency makes its AFPPH determinations or structures its regulatory actions to avoid being arbitrary or capricious. In many cases, real world examples of similarly regulated tobacco products or MRTP claims are sparse or nonexistent, or other relevant research and evidence is inadequate or incomplete or cannot be fully developed. More fundamentally, no matter how much relevant information is available, trying to predict how different members of the tobacco industry will respond to a PMTA or MRTP order and the new marketing of the related product (including possible new legal challenges or lobbying) will always be uncertain and imprecise—as will efforts to predict how different youth and adult users and nonusers will respond to the product's marketing under the new order and to the industry's related actions. Here, too, FDA could exercise its discretion to address this gap in the TCA (in a not arbitrary or capricious way) by acknowledging these uncertainty challenges and providing a reasonable explanation for how it is handling them. So far, however, FDA has made its PMTA and MRTP AFPPH and related order decisions in an ad-hoc, case-by-case way, without clearly identifying or discussing these uncertainty issues and without developing any specific practices and procedures for addressing them constructively. Nor has FDA provided any reasonable explanation or justification for how it has actually made its AFPPH determinations and structured its PMTA and MRTP orders despite facing these uncertainty challenges.[26]

These gaps in the legal framework provided by the TCA, and the considerable not-yet-exercised discretion given to FDA to determine how to address them, provide a major opportunity for ethical analyses to provide constructive guidance as to:

(1) How FDA could most ethically evaluate PMTA and MRTP applications given inevitable uncertainties in predicting future public health, subpopulation health, and other ethically relevant impacts;
(2) How FDA could most ethically clarify and apply the AFPPH standard in the context of PMTA and MRTP applications; and
(3) How FDA could most ethically structure any permissive PMTA or MRTP orders it issues.

II. DEVELOPING REASONABLE ESTIMATES OF THE FUTURE IMPACTS OF PMTA AND MRTP ORDERS TO MAKE ETHICAL ANALYSES POSSIBLE

To evaluate possible permissive PMTA and MRTP orders to ensure that they are both AFPPH and ethically appropriate, FDA would need to identify their future impacts that would determine their net public health impact or otherwise be ethically relevant and then develop reasonable estimates of the likelihood and size of those future impacts. Despite the practical difficulties and inevitable uncertainties involved,

[26] For a discussion of the uncertainty problems in making AFPPH determinations in the context of PMTA and MRTP applications and how FDA has and has not addressed those issues, see Lindblom, *supra* note 6, at 46–47. For a more general discussion of how FDA could, should, and has handled the uncertainties problem in the context of making AFPPH decisions, see Lindblom, *supra* note 20, at 560–62.

FDA could legally and ethically exercise its discretion to rely on any reasonable, not-arbitrary-or-capricious method for using available data, knowledge, and expertise to identify and estimate the future relevant impacts—so long as FDA provided a reasonable explanation for its related choices and actions. So far, FDA has not done that, but the agency certainly could.

For example, FDA might reasonably determine that using estimated impacts on reduced mortality, increases in life years, or increases in quality adjusted life years (QALYs) were valid proxies for quantifying a PMTA or MRTP order's future health impacts, both among the population as a whole and among different subpopulations, such as youth, adults, users, nonusers, or certain disadvantaged versus advantaged groups.[27] Then FDA could determine that it was reasonable to project those impacts through using relevant experts' worst-case, best-case, and most-likely-case estimates (based on available research, data, and other evidence) relating to the major factors creating such mortality or life-year impacts, such as the extent to which the order would prompt different harm-increasing or harm-reducing behavior changes among different subpopulations (including considerations of different ways the industry might react to the rule to influence consumer behaviors), or what the mortality or life-year gains or losses would be among different subpopulations and overall from the different behavior changes. FDA could develop these evidence-based expert estimates by having its own tobacco control experts or relevant outside experts review available relevant data, research, and analysis before developing consensus worse-, best-, and most-likely-case estimates. Or estimated ranges of relevant health impacts and probabilities could be developed through more formal and detailed modeling, with formal expert elicitations or other reasonable procedures used to develop any of the model's needed inputs that had uncertain values that could not otherwise be reasonably quantified.[28]

Consultations with relevant experts could also identify the major ethically relevant non-health harms and risks that the various rules might produce. Quantifying estimated possible impacts on personal autonomy, happiness, or overall wellbeing or other non-health impacts would be more difficult, compared to estimating mortality, life-year, or QALY impacts.[29] Nevertheless, FDA could still reasonably use the procedures outlined here at least to estimate the numbers of people in different relevant subpopulations who might have their non-health happiness or wellbeing affected in various identified and described positive or negative ways under best-case, worst-case, and most-likely-case scenarios.

Although imperfect, such procedures to identify and estimate the impacts of the rule options on the public health and on the health of relevant subpopulations, as well as other ethically relevant impacts, would enable FDA to move forward in a reasonable

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[27] *See, e.g.*, Yves Arrighi et al., *To Count or Not to Count Deaths: Reranking Effects in Health Distribution Evaluation*, 24 HEALTH ECON. 193 (2015); John La Puma & Edward F. Lawlor, *Quality-Adjusted Life-Years: Ethical Implications for Physicians and Policymakers*, 263 JAMA 2917 (1990).

[28] *See, e.g.*, Benjamin J. Apelberg et al., *Potential Public Health Effects of Reducing Nicotine Levels in Cigarettes in the United States*, 378 NEW ENG. J. MED. 1725 (2018); David T. Levy et al., *Modeling the Future Effects of a Menthol Ban on Smoking Prevalence and Smoking-Attributable Deaths in the United States*, 101 AM. J. PUB. HEALTH 1236 (2011); M. Granger Morgan, *Use (and Abuse) of Expert Elicitation in Support of Decision Making for Public Policy*, 111 PROC. NAT. ACAD. SCI. USA 7176 (2014).

[29] *But see, e.g.*, Steven J. Firth, *The Quality Adjusted Life Year: A Total-Utility Perspective*, 27 CAMBRIDGE Q. HEALTHCARE ETHICS 284 (2018) (arguing that a utilitarian response should quantify non-health impacts like individual and social utility).

way to evaluate PMTA and MRTP applications, make related AFPPH determinations (regardless of how FDA or the courts clarify and refine the standard), and otherwise do all the agency could to ensure that any final permissive PMTA or MRTP orders are both AFPPH and ethically appropriate.

III. HOW RISKY AND HARMFUL COULD AN FDA PMTA OR MRTP ORDER BE AND STILL BE AFPPH?

The major remaining ambiguity in the AFPPH standard in this context is the extent to which a permissive PMTA or MRTP order could create a risk of a net public health harm or produce new individual or subpopulation harms and still be AFPPH. To date, however, all of FDA's permissive PMTA and MRTP orders have anticipated the possibility that the orders might produce net public health harms or that the marketing of the subject product might otherwise turn out to be not AFPPH.[30] In addition, FDA clearly anticipated that each of the orders would produce some brand-new health harms and risks.[31] Accordingly, FDA has been implicitly using an interpretation of the AFPPH standard that, in at least some situations, allows new tobacco products or MRTP claims on the market even if they could create new individual or subpopulation health harms or might produce a negative net impact on the overall public health. Indeed, it is difficult to imagine that allowing any new tobacco product or MRTP claim on the market would not create such new harms and risks, at least to some extent, given the manufacturers' core goal of maximizing profits, which can be done most directly and easily through increasing overall sales and use, whether it reduces or increases health harms and risks.[32]

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[30] For example, the IQOS Final PMTA Order stated that compliance with its requirements "is not a guarantee that the marketing of the products will remain appropriate for the protection of the public health, particularly if, despite these measures, there is a significant uptake in youth initiation." FOOD & DRUG ADMIN., *Marketing Order Letter to Philip Morris Products S.A.* 1 (April 30, 2019) [hereinafter IQOS Final PMTA Order]. Anticipating the possibility of unexpected negative impacts, all the permissive PMTA and MRTP orders issued to date have also required a range of post-market surveillance and reporting regarding new research, consumer behaviors, and other matters to "help FDA determine whether continued marketing of [the] product is appropriate for the protection of the public health or whether there are or may be grounds for withdrawing or temporarily suspending [the permissive] order." FOOD & DRUG ADMIN., *Marketing Order Letter to Swedish Match* 3–4 (Nov. 10, 2015) [hereinafter Snus Final PMTA Orders]. The IQOS Final PMTA Order has similar text, in addition to a Final MRTP Order for Snus. FOOD & DRUG ADMIN., *Modified Risk Granted Orders Letter to Swedish Match USA, Inc.* 8, 11, 14 (Oct. 22, 2019) [hereinafter Snus Final MRTP Order]; *see also* IQOS Final PMTA Order at 9. *See also* Lindblom, *supra* note 6, at 12, 13, 18, 19, 21. FDA PMTA final orders and decision summaries are available at FDA's website, along with FDA MRTP final orders and decision summaries. *Modified Risk Orders*, *supra* note 5; *Premarket Tobacco Product Marketing Orders*, *supra* note 5.

[31] For example, FDA concluded that current evidence indicated that IQOS uptake among youth and nonsmokers would occur, but be low, although "the potential for rapid uptake of a novel tobacco product among youth exists." *PMTA Coversheet: Technical Project Lead Review (TPL)*, FOOD & DRUG ADMIN. 76 (2019) [hereinafter IQOS PMTA Decision Summary]; s*ee also Scientific Review of Modified Risk Tobacco Product Application (MRTPA) Under Section 911 (d) of the FD&C Act—Technical Project Lead*, FOOD & DRUG ADMIN. 13, 45 (2019) [hereinafter Snus MRTP Decision Summary]; Lindblom, *supra* note 6.

[32] For example, if offered a less-harmful PMTA or MRTP alternative to smoking, at least some smokers who would otherwise quit would switch to the new product or engage in dual use instead; some former smokers who would not otherwise relapse would start using the new product; and some youth and young adults who would not otherwise use any tobacco product would try the new PMTA or MRTP product and become regular, addicted users. At the same time, the product would almost certainly be addictive (as few addicted smokers would be likely to switch to a less-harmful option that did not feed their addiction)

However, FDA has not provided any explanation or justification for interpreting and applying the AFPPH standard to allow PMTA or MRTP orders to create new health harms or a risk of a negative net public health impact. Nor has FDA otherwise clarified its interpretation of the AFPPH standard or how it applies in these specific situations. In particular, FDA has not even stated that the likelihood and size of expected or desired net public health gains must be larger than the likelihood and size of the possible negative net public health impacts for a PMTA or MRTP order to be AFPPH.[33] Nor has FDA explained in even general terms how large it thinks the expected health gains must be, compared to the expected or possible new health harms, to make a PMTA or MRTP order AFPPH.[34]

Accordingly, FDA still needs to exercise its discretion, within the constraints of the TCA and the not-arbitrary-or-capricious standard, to clarify the remaining gray areas of the AFPPH standard in the context of PMTA and MRTP applications and orders.[35] To explore how FDA might do that in the most ethically appropriate way, we can start with the fundamental gray area question: Could it be ethically appropriate to consider a permissive PMTA or MRTP order AFPPH if it creates a non-trivial risk of producing

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and would still be harmful, because it would contain either consumable tobacco or nicotine. *See generally*, *e.g.*, Drug and Therapeutics Bulletin, *Republished: Nicotine and Health*, 349 BMJ 1 (2014).

[33] In a public presentation, a senior staff person from FDA's Center for Tobacco Products stated that, in the context of FDA determinations relating to whether to allow a new tobacco product on the market, "[a]lthough there is not a regulatory definition, FDA considers a product 'Appropriate for Protection of the Public Health' (APPH) if we determine marketing of the product has the potential to result in decreasing morbidity and/or mortality." Priscilla Callahan-Lyon, Deputy Dir., Div. of Individual Health Sci., FDA Ctr. for Tobacco Prods., Presentation at Food & Drug Law Institute Tobacco and Nicotine Products Regulation and Policy Conference: The ENDS Guidance, IQOS Marketing Authorization, and the Future of Premarket Tobacco Applications: The FDA Perspective 18 (Oct. 25, 2019), https://www.fdli.org/wp-content/uploads/2019/10/945-1030-Premarket-Tobacco.pdf [https://perma.cc/J6YK-ZZ4P]. But nothing was said as to whether FDA believed that potential must be larger than the potential that it would increase morbidity and/or mortality instead. *Id.*

[34] It is also not possible to imply or reverse engineer any such ratios or contrasts from the permissive snus or IQOS PMTA or MRTP orders or decision summaries because they do not identify all the different ways the marketing of the products under the orders could produce harm reductions and harm increases and do not provide any estimates or comparisons of the risk of new harms versus the likelihood of new harm reductions. *See* IQOS Final PMTA Order, *supra* note 30; Snus Final PMTA Orders; *supra* note 30; Snus Final MRTP Order, *supra* note 30. *See also* IQOS PMTA Decision Summary, *supra* note 3; Snus MRTP Decision Summary, *supra* note 31; Lindblom, *supra* note 6, at 13. Accordingly, it does not appear that FDA has, behind the scenes, completed its analysis of the AFPPH standard and developed clarifications of its remaining gray areas, but simply not yet made its conclusions and underlying rationale public.

[35] A standard principle of statutory interpretation states that Congress would not have included a provision or process in a statute unless Congress expected that provision or process to be used, which could suggest that Congress expected FDA to determine that it would be AFPPH to issue permissive PMTA or MRTP orders for at least some new tobacco products under some conditions. But it is also quite possible that Congress did not know whether any products would or could actually qualify for permissive PMTA or MRTP orders but wanted to enable FDA to make that determination on an AFPPH basis. Indeed, the legislative history shows that the possibility that no applicants would be able to secure permissive PMTA orders was directly considered. 155 CONG. REC. S6004-05 (daily ed. June 3, 2009) (statement of Sen. Burr). At the same time, the Act and its legislative history make it clear that FDA is not even allowed to consider any arguments regarding personal autonomy or any alleged smokers' rights to have access to less-harmful alternatives when making decisions as to whether it would be AFPPH to issue any PMTA or MRTP orders. Lindblom, *supra* note 20, at 538–39.

a significant net harm to the public health instead of its expected or desired net reduction to the health harms and risks to the population as a whole?[36]

Despite its non-malfeasance (or "do no harm") principle, bioethics regularly justifies medical treatments that cause serious side effects or create risks of serious harms, sometimes including death, when necessary to cure the patient or otherwise prevent or reduce severe health harms or death.[37] Similarly, FDA regularly approves drugs as "safe and effective" for the prevention or treatment of certain medical problems even when they also produce harmful side effects or create risks of serious harms or death.[38] A parallel approach suggests that issuing a PMTA or MRTP order to improve the public health could be ethically acceptable as AFPPH even if it also creates an unavoidable smaller risk of producing a net public health harm, but only if:

(1) Alternative, less harmful or risky ways to secure the net public health gains
are not available;
(2) The risk of a net public health harm is necessary to make securing the net gains possible;
(3) All readily available measures have been employed to reduce the order's public health risks and reduce any new individual or subpopulation health harms and risks caused by the order (at least to the extent possible without reducing the likelihood and size of its public health gains); and
(4) The public health gains are significantly more likely and larger than the possible harms.

Yet FDA has clear authority and sufficient resources to issue tobacco control rules that would secure much larger and more rapid net public health gains than any PMTA or MRTP order could possibly secure, without any risk of producing a negative net public health impact.[39] It is also likely that FDA could secure larger and less risky declines in tobacco-related harms and risks through taking other available actions, such as initiating additional public education campaigns or more aggressively enforcing existing TCA and rule restrictions on tobacco products and their labeling, marketing, distribution, and sale. Issuing such rules and taking these other actions to reduce tobacco-related harms without any significant downside health risks would be

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[36] The use of the terms "non-trivial" and "significant" here mean to acknowledge only that certain estimated statistical probabilities and estimated negative public health impacts could be both impossible to avoid and so tiny as to be no different than zero for all practical purposes. Exactly how large a risk could be before becoming "non-trivial" and how large a net public health harm could be before becoming "significant" are ethical questions that will be addressed in the following analysis.

[37] *See, e.g.*, Raanan Gillon, *"Primum Non Nocere" and the Principle of Non-Maleficence*, 291 BRITISH MED. J. 130 (1985); Peter F. Omonzejele, *Obligation of Non-Maleficence: Moral Dilemma in Physician-Patient Relationship*, 4 J. MED. & BIOMEDICAL RES. 22 (2005).

[38] *See*, *e.g.*, Arthur A. Ciociola et al., *How Drugs are Developed and Approved by the FDA: Current Process and Future Directions*, 109 AM. J. GASTROENTEROLOGY 620, 623 (2014); Donald W. Light et al., *Institutional Corruption of Pharmaceuticals and the Myth of Safe and Effective Drugs*, 41 J.L. MED. ETHICS 590 (2013).

[39] *See*, *e.g.*, Eric N. Lindblom, *What Tobacco Control Rules Would an Ethically Responsible FDA Implement (If the White House Would Let It)? Would a Nicotine-Reduction Rule Pass Muster?* (in press) (on file with author).

much more AFPPH and ethically appropriate than issuing any PMTA or MRTP orders that produce similar or considerably smaller potential health gains but create serious risks of producing new underlying health harms or even negative net public health impacts. Indeed, those available, much more AFPPH options for reducing tobacco-related health harms could make issuing any PMTA or MRTP orders not AFPPH (or make issuing them arbitrary or capricious). An ethical argument could still be made, however, that issuing certain PMTA or MRTP orders might be AFPPH if doing so would accelerate or increase the declines in tobacco use harms FDA could readily secure by only issuing tobacco control rules or taking other available actions. In addition, because of bureaucratic obstacles and inadequate White House support, FDA has not been able to issue any major substantive rules to quickly or sharply reduce tobacco-related harms since receiving its extensive tobacco control powers in 2009.[40] If those constraints continue, FDA efforts to secure tobacco-related public health gains by issuing potentially harmful PMTA or MRTP orders could more easily qualify as ethically AFPPH.[41]

To be ethically AFPPH, however, the risks to the public health and any underlying new individual or subpopulation health harms created by the orders would still have to be necessary for making their expected public health gains possible. That means FDA would have to ensure that the final orders included all readily available restrictions, requirements, and other means to minimize the likelihood and size of any public health risk or negative individual or subpopulation health impacts the orders might produce, at least to the extent that doing so would not significantly reduce the likelihood or size of the orders' expected net public health gains or increase the likelihood and size of its possible net public health harms.[42] FDA could evaluate the orders proposed in the PMTA and MRTP applications and develop improvements to

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[40] *Id.* Pursuant to a court order, in March 2020 FDA issued a final rule to require graphic health warnings on all cigarette packs. But that rule will not go into effect until October 16, 2020 (if industry legal challenges are not successful). Am. Acad. of Pediatrics v. FDA, 330 F. Supp. 3d 657 (D. Mass. 2018); *Cigarette Labeling and Health Warning Requirements*, FOOD & DRUG ADMIN. (June 17, 2020), https://www.fda.gov/tobacco-products/labeling-and-warning-statements-tobacco-products/cigarette-labeling-and-health-warning-requirements [https://perma.cc/Y8BX-RHA6]. In addition, like even stronger graphic health warning requirements throughout the world, the new FDA-required warnings will have only a marginal impact on smoking and overall tobacco use harms. *See, e.g.*, Seth M. Noar et al., *The Impact of Strengthening Cigarette Pack Warnings: Systematic Review of Longitudinal Observational Studies*, 164 SOC. SCI. & MED. 118 (Sept. 2016), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5026824/ [https://perma.cc/DQL7-QWWS]. In fact, FDA issued the rule only to increase public understanding of the negative health consequences of cigarette smoking, not to reduce smoking or related harms. Tobacco Products; Required Warnings for Cigarette Packages and Advertisements, 85 Fed. Reg. 15,638, 15,638–39 (issued Mar. 18, 2020).

[41] However, any evaluation of the possible public health gains from issuing PMTA or MRTP orders would still need to take into account whatever tobacco control rules FDA is allowed to implement, along with any other tobacco control actions by FDA or other government or non-government entities, including any not yet in effect but certain to be implemented in the not too distant future.

[42] For example, allowing an e-cigarette on the market in ways that would reduce the number of quality-adjusted life years (QALYs) lost to tobacco-nicotine use by an estimated 10,000 through increasing the QALYs among smokers who switched by 15,000 and reducing the QALYs among other users by 5,000 would be much less desirable, from a public health or ethical perspective, than securing that same 10,000 reduction in lost QALYs by increasing the QALYs among the switching smokers by 10,000 and not reducing the QALYs among any other users at all. For FDA's parallel duty under the APA's not-arbitrary-or-capricious standard to take advantage of any readily available ways to revise a regulatory action to reduce any related costs or other equally or more serious negative impact, unless that would interfere with its ability to achieve statutory purposes. *See supra* notes 23–24 and accompanying text.

any permissive final orders through its own expertise or from consulting with outside experts. In addition, FDA could seek comments from any interested parties through setting up public dockets relating to all PMTA and MRTP applications and possible final orders.[43]

After all available, constructive improvements to a possible final order were made, it still remains unclear as to how much larger the likelihood and size of the expected net public health gains would need to be, compared to the likelihood or size of the possible negative net public health impacts, for the order to be considered both AFPPH and otherwise ethically appropriate.[44] While the ethical perspectives do not support any specific ratio, they, along with common sense, suggest that the following should come into play in any such evaluation:

(1) How large and severe might the net public health harms be? Even a quite small risk of a major public health fiasco might be ethically too large, regardless of the possible public health gains that would more likely be secured instead;
(2) What is the timing of the possible new health gains and harms from the order? If the order's expected near-term health gains (e.g., through smokers switching to less-harmful PMTA or MRTP products) would primarily be threatened by possible future health harms (e.g., from the products increasing youth initiation with related harms not occurring until the users are older adults), FDA would have time to intervene and prevent or reduce those future harms (e.g., if much smaller amounts of smoker switching than anticipated occurred or if much larger than anticipated youth initiation occurred);
(3) Would FDA realistically be able and likely to take prompt action to prevent or stop the future public health harms from occurring (either generally or in response to the product's marketing not prompting the anticipated smoker switching or increasing new initiation more than expected)? For example, might White House

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[43] The TCA requires FDA to seek public comments on MRTP, but not PMTA, applications, and says nothing about FDA seeking comments on proposed MRTP or PMTA orders. TCA § 911(e), 21 U.S.C. § 387k(e) (2018). Although some redactions or other modifications might be necessary to protect any confidential and proprietary business information of the applicants that they did not want disclosed, FDA could establish a notice-and-comment procedure for receiving comments on applications for PMTA orders similar to the process it uses for MRTP applications and could also make its proposed permissive final PMTA or MRTP orders available for public comment, along with their draft decision summaries or other order justifications, before issuing them in final form.

[44] This ratio might be estimated by comparing the product of the likelihood of the expected net public health gain times its size to the likelihood of the possible negative net public health impact times its size. For example, if an order were reasonably estimated to produce a 50% to 75% chance of producing a net gain of 50 to 100 thousand life years (or QALYs) that would otherwise have been lost to smoking or other tobacco use but also created a 25% to 50% chance of producing a new net loss of an additional 10,000 to 25,000 life years, the possible overall gains (probability times size) would range from 25,000 to 75,000 life years and the possible overall losses (probability times size) would range from 2,500 to 12,500 life years—and 25,000 to 75,000 is larger than 2,500 to 12,500. For an example of such a utilitarian approach when determining which of several drugs to prescribe that have different potential benefits and risks, see Elinor Mason, *Objectivism, Subjectivism, and Prospectivism, in* THE CAMBRIDGE COMPANION TO UTILITARIANISM 184 (Ben Eggleston & Dale E. Miller eds., Cambridge Univ. Press, 2014).

political concerns or bureaucratic obstacles stop or delay an FDA effort to rescind the order and pull the product from the market?[45];

(4) Would the health gains, harms, and risks from the order be distributed broadly in an impartial, non-discriminatory manner? Or would the likely health gains primarily benefit already advantaged subpopulations, thereby increasing inequitable health disparities, or would the health harms and risks primarily harm disadvantaged and vulnerable subpopulations, thereby increasing health disparities?; and

(5) Would the possible public health harms be a direct consequence from FDA issuing the order and the marketing of the related product, or would they come from intervening events where competent adults made informed, autonomous choices to run the personal health risks causing the net public health harms?

Considering these factors would inform any effort to determine whether the potential public health benefits from a possible PMTA or MRTP order ethically outweigh its possible public health harms, thereby making the order ethically AFPPH. But they do not provide clear ethical guidance for how FDA should make final AFPPH determinations when the likelihood and size of the probable public health gains and possible harms and the other ethical considerations are not so extremely positive or negative to make the decision obvious. Nor do the ethical perspectives, themselves,

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[45] FDA has both a statutory and an ethical duty to put post-market surveillance systems in place to identify any negative public health impacts from a PMTA or MRTP order (which FDA has generally done in its permissive PMTA and MRTP orders) so that FDA could quickly take remedial action when unexpected, inappropriate harms occur. It is worth noting, however, that despite enormous increases in youth initiation into e-cigarette use (including initiation by youth who would not otherwise have used any tobacco or nicotine product), FDA still did not take any major rulemaking or enforcement action to prevent or reduce youth use through the end of 2019, despite identifying and labeling it as a public health crisis in 2018. *Statement from FDA Commissioner Scott Gottlieb, M.D., On Meetings with Industry Related to the Agency's Ongoing Policy Commitment to Firmly Address Rising Epidemic Rates in Youth E-Cigarette Use*, FOOD & DRUG ADMIN. (Oct. 31, 2018), https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-meetings-industry-related-agencys-ongoing-policy [https://perma.cc/XLS7-GA24]. While FDA did finally take some enforcement action against some flavored e-cigarettes in early 2020 to try to prevent and reduce youth use, that effort left many flavored e-cigarettes completely unrestricted, and FDA has still not proposed any new rules to prevent or reduce youth use. *Enforcement Priorities for Electronic Nicotine Delivery Systems (ENDS) and Other Deemed Products on the Market Without Premarket Authorization*, FOOD & DRUG ADMIN. (Jan. 2020), https://www.fda.gov/media/133880/download [https://perma.cc/E5VL-9CGH]. FDA did, however, launch a public education campaign to address youth e-cigarette use in July 2019. Press Announcement, *FDA Launches Its First Youth E-Cigarette Prevention TV Ads, Plans New Educational Resources as Agency Approaches One-Year Anniversary of Public Education Campaign*, FOOD & DRUG ADMIN. (July 22, 2019), https://www.fda.gov/news-events/press-announcements/fda-launches-its-first-youth-e-cigarette-prevention-tv-ads-plans-new-educational-resources-agency [https://perma.cc/TJ98-AQQG]. FDA's ability to initiate a public education campaign, while being unable to issue any related rules or take more constructive enforcement action, appears to be because of White House interference with its enforcement actions and rulemaking, which has not yet extended to interfering with FDA educational efforts. *See, e.g.*, Ann Karni et al., *Trump Retreats from Flavor Ban for E-Cigarettes*, N.Y. TIMES (Nov. 17, 2019), https://www.nytimes.com/2019/11/17/health/trump-vaping-ban.html?auth=login-email&login=email [https://perma.cc/8N3R-BNDU]; *see also infra* notes 91–92 and accompanying text; Kalle Grill, *Tobacco Control vs. E-Cigarettes: The Long-Term Liberal Perspective*, NICOTINE & TOBACCO RES. (2020), https://academic.oup.com/ntr/advance-ar0ticle/doi/10.1093/ntr/ntaa085/5846158 [https://perma.cc/R34Q-EZ83] (on the ethical issues from accepting longer-term less-harmful e-cigarette use to secure shorter-term reductions to smoking).

provide any clear guidance as to how FDA should ethically determine whether a possible PMTA or MRTP order is AFPPH in closer cases. A related possibility, however, would be for FDA to try to determine whether rational people evaluating the potential PMTA or MRTP order from a Rawlsian original position behind a veil of ignorance (e.g., not knowing whether they would be a person possibly benefited or put at risk by the order but understanding that they could be either) would, after considering the factors outlined above, find that the public health risks from the order were worth running to have a chance at securing its potential public health gains.[46]

Although there does not appear to be any bright-line test or clear criteria for determining which ratios of probable public health gains to possible public health harms should or should not ethically be considered AFPPH, FDA could follow the analysis provided here to develop bright-line *minimum* standards that PMTA and MRTP applications must meet to merit further consideration. To start, FDA would explain that it has determined that a PMTA or MRTP order cannot possibly be AFPPH unless, at a minimum:

> (1) All reasonable steps have been taken to design and manufacture the subject product to make it as minimally harmful as possible (without interfering with its ability to serve as a complete substitute for more harmful tobacco products)—thereby maximizing the harm reductions from users of more-harmful products switching completely to the subject product and minimizing the new harms from all other uses of the product;
> (2) All reasonably available restrictions or requirements on the product's packaging, labeling, marketing, and sale that would prevent or reduce harm-increasing uses of the product (without increasing net harms by also decreasing harm-reducing uses) are included in the final PMTA or MRTP order; and
> (3) Reasonable estimates indicate that issuing the order is clearly more likely to produce a net public health gain than a net public health loss and the overall probable gain (likelihood times size) is larger than the overall possible loss (likelihood times size).

FDA would then specifically require applications to: show that they have acted accordingly to minimize the harmfulness of the subject products and include constructive restrictions and requirements in their proposed orders; present estimates of all the possible health gains and losses the order might produce (measured in life years or QALYs); and provide related evidence indicating that issuing the permissive order they propose would produce a greater likelihood of a net public health gain than a public health loss and that the overall probable gain would be larger than the overall

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[46] JOHN RAWLS, A THEORY OF JUSTICE (1971). *But see* Carlos Soto, *The Veil of Ignorance and Health Resource Allocation*, 37 J. MED. & PHILOSOPHY 387 (July 2012), https://pubmed.ncbi.nlm.nih.gov/22832181/ [https://perma.cc/SR7M-BUJ8]. FDA could even put a group of relevant public health or ethics experts, or a random sample of smokers and parents, through a carefully administered veil-of-ignorance process to see whether certain risks vs. benefits would or would not be seen as acceptable after considering all the relevant factors. *See, e.g.*, Fredrik Andersson & Carl H. Lyttkens, *Preferences for Equity in Health Behind a Veil of Ignorance*, 8 HEALTH ECONS. 369 (1999), https://pubmed.ncbi.nlm.nih.gov/10470544/ [https://perma.cc/296R-MHUW].

possible loss, perhaps by using formal expert elicitations and related modeling.[47] To support FDA's further evaluation of applications that qualify, FDA would also require applicants to provide evidence, estimates, and analysis relating to all of the previously outlined relevant ethical factors.[48]

Upon receiving PMTA and MRTP applications, FDA could then reject any that did not exhibit a good faith effort to structure the product and proposed order in this way, did not provide the related information and analysis, or did not provide any indication that a final order for the subject product could possibly produce net public health gains that would be significantly larger and more likely than its possible net public health harms. But FDA would also have an ethical duty to fix any not-AFPPH orders proposed by a PMTA or MRTP application (rather than just reject the application) whenever doing so clearly offered FDA an opportunity to accelerate or increase reductions in tobacco-related harms beyond what FDA could accomplish without fixing the order.[49]

At the same time, it is clear from the statute that the primary purpose of the PMTA and MRTP provisions is to protect the public health by preventing potentially harm-increasing tobacco products or relative-risk claims from entering the market.[50]

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[47] Or FDA might go further and require that the applicants use the most pessimistic ends of the estimated ranges when making these calculations and show that the probable net public health gains would be at least some multiple of the size of the possible net public health losses. Such bright-line tests by regulatory agencies, even when not precisely supported by available research or other evidence, have been upheld by the courts based on the need to provide clear standards and simplify administration and enforcement. Found. v. FCC, 776 F.3d 21, 28 (D.C. Cir. 2015); *see also* Actavis Elizabeth LLC v. FDA, 625 F.3d 760, 766 (D.C. Cir. 2010) ("[A]gencies may employ bright-line rules for reasons of administrative convenience, so long as those rules fall within a zone of reasonableness and are reasonably explained." (internal quotes and citations omitted)); Ohio v. U.S. Army Corps of Eng'rs (In re EPA & DOD Final Rule), 803 F.3d 804, 807–08 (6th Cir. 2015); Macon Cty. Samaritan Mem'l Hosp. v. Shalala, 7 F.3d 762, 768 (8th Cir. 1993) ("[B]right-line tests are a fact of regulatory life.").

[48] FDA has issued a Proposed Final Rule for PMTA applications, but it does not require that applications make any of these showings. Premarket Tobacco Product Applications and Recordkeeping Requirements, 84 Fed. Reg. 50,566 (proposed Sept. 25, 2019). Nor does FDA's final Guidance for e-cigarette PMTAs suggest that applications make any of these showings. *Premarket Tobacco Product Applications for Electronic Nicotine Systems: Guidance for Industry*, FOOD & DRUG ADMIN. (2019), https://www.fda.gov/media/127853/download [https://perma.cc/FHP7-BCN5].

[49] As noted above, the burden of proof is on the applicant to provide sufficient evidence and analysis to enable FDA to find that issuing a permissive PMTA or MRTP final order is AFPPH. TCA § 910(c)(2), 21 U.S.C. § 387j (c)(2) (2018); TCA § 911(g)(1), (2) & (3)(A), 21 U.S.C. § 387k(g)(1), (2) & (3)(A). So FDA has no legal duty to fix deficient applications or fix deficient proposed final orders instead of rejecting them.

[50] TCA § 2, Findings (36)–(44), 21 U.S.C. § 387 note (2018); *id.* § 3, Purpose (4), 21 U.S.C. § 387 note; *id.* § 910, 21 U.S.C. § 387j; *id.* § 911, 21 U.S.C. § 387k. One might also argue that the ethical "precautionary principle" supports not letting new products or new MRTP claims on the market before their potential harmfulness to the public health is fully understood (rather than letting them on the market and then taking them off only if and when they cause new net public health harms). *See, e.g.*, Ashley M. Bush et al., *Employing the Precautionary Principle to Evaluate the Use of E-Cigarettes*, 4 FRONTIERS PUB. HEALTH 5 (2016); *see also* Marco Martuzzi, *The Precautionary Principle: In Action for Public Health*, 64 OCCUPATIONAL ENVTL. MED. 569 (2007). However, the precautionary principle, if it applies at all, would apply quite weakly here, where the PMTA or MRTP order has already been reasonably estimated to have a greater potential to produce net public health gains than net public health losses, FDA has already taken all readily available steps to structure the order to minimize all risks to the public health (that do not reduce its potential public health gains), and FDA has confirmed that the PMTA or MRTP order has the potential to accelerate or maximize reductions to tobacco-related public health harms (i.e., other options available to FDA will not reduce tobacco-related harms as quickly and sharply as possible by themselves).

Accordingly, once FDA has modified any promising possible final PMTA or MRTP orders to make them as ethically AFPPH as possible, FDA must be quite conservative or cautious about issuing permissive PMTA or MRTP orders that are not obviously AFPPH because of the public health risks they create. When dealing with such difficult cases, FDA could honor its statutory duty to err on the side of protecting the public health in the PMTA/MRTP context by basing is AFPPH evaluation on only the more pessimistic reasonably derived expert estimates of the likelihood and size of the probable net public health gains and the possible net losses.[51] In addition, prior to issuing any final order, FDA would benefit from seeking additional insights from outside public health and ethics experts and other interested parties. Among other efforts, FDA should use standard notice-and-comment procedures to provide drafts of the permissive PMTA or MRTP orders it is considering, along with the evidence-based expert estimates it develops of the likelihood and size of the probable net public health gains and possible net public health harms from the orders and any other related information or analyses it develops or secures, and specifically ask interested parties to comment on whether running the estimated risks to secure the estimated benefits should be considered AFPPH. After doing that, and otherwise following all the procedures described here, FDA could follow the primarily defensive purpose of the PMTA and MRTP provisions by not issuing any permissive PMTA or MRTP order that FDA believed the courts might possibly strike down as arbitrary or capricious or not AFPPH, or that still left FDA with any doubts as to whether its probable net public health gains clearly justified its more probable net public health losses.

As previously discussed, all of these efforts relating to PMTA and MRTP applications would be unnecessary if FDA were able to use its extensive tobacco control authorities and resources to implement substantive rules and take other actions to reduce tobacco-related health harms and risks more quickly and sharply (with no risks of producing public health losses). If FDA could do that, and FDA determined that issuing permissive PMTA and MRTP orders (with their public health risks) could not accelerate or minimize the public health gains, then no PMTA or MRTP order could be ethically found AFPPH. Assuming that political and bureaucratic impediments make that kind of less-risky and more powerful FDA tobacco control action unlikely, and that PMTA and MRTP applications offer FDA the possibly of issuing permissive ethically AFPPH final orders, a remaining challenge for FDA will be how to make the final AFPPH orders as ethically appropriate as possible, as well.

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[51] For example, if FDA used an expert elicitation to develop consensus or averaged estimated ranges of the likelihood and size of the probably net public health gains and possible net harms from a possible PMTA or MRTP order (measured in life years or QALYs), FDA could evaluate the possible order based on only the low end of the ranges for the likelihood and size of the probable net gains and the high end of the ranges for the likelihood and size of the possible harms. The proposal here is not to use the most pessimistic expert's estimates, but the most pessimistic ends of the estimated ranges of likelihoods and sizes that are developed from averaging or otherwise consolidating the estimates and insights from a diverse selection of relevant experts. A similar process could be used for using the more pessimistic or protective estimates of other relevant factors (e.g., potential impacts on vulnerable or disadvantaged subpopulations) that need to be considered to evaluate the acceptability of running the estimated risks to the public health to secure the estimated gains.

IV. HOW COULD FDA STRUCTURE ITS PMTA AND MRTP ORDERS TO BE AS AFPPH AND OTHERWISE ETHICALLY APPROPRIATE AS POSSIBLE?

Based on the preceding analysis, the most ethically appropriate, legally viable, AFPPH PMTA or MRTP order, based on the ethical perspectives being applied here, would:

(1) Secure the largest possible amount of public health gains through reducing tobacco-related health harms and risks.
(2) Not create any risk of producing a negative net public health impact.
(3) Not produce any new health harms or risks, especially not among already disadvantaged or vulnerable subpopulations.
(4) Reduce, or at least not increase, inequitable disparities.
(5) Increase, or at least not reduce, personal autonomy.
(6) Reduce, or at least not increase, any other ethically relevant non-health harms or inequities.
(7) Increase, or at least not reduce, any other ethically relevant non-health benefits, especially among any disadvantaged or vulnerable subpopulations.

While the sixth and seventh criteria might appear quite open ended, bioethics and public health ethics for the most part show little concern for any specific, substantive, non-health harms or impacts, beyond their concerns for personal autonomy—except to the extent that those non-health impacts might also have an effect on the public health, individual health, health disparities, or personal autonomy (and the concern over personal autonomy in public health ethics is quite weak compared to its public health priority).[52] Utilitarianism, however, looks well beyond just health, with its focus on producing the greatest *good* for the greatest number being concerned with not only health impacts but any other impacts that have a significant effect on individual people's happiness, pleasure, or overall wellbeing.[53] In addition, ethical concerns have specifically been raised about initiatives that de-normalize smoking and thereby alienate, shame, or stigmatize smokers, which can harm their health and otherwise reduce their general wellbeing, interfere with concepts of justice or equity by having a disproportionate negative effect on disadvantaged or vulnerable subpopulations, or prompt policymakers and others to have less respect for the stigmatized smokers' individual autonomy or human rights.[54]

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[52] *See supra* notes 8–9.

[53] *See supra* note 7. Given the necessity of avoiding death to be able to experience happiness, pleasure, or wellbeing, and the key role of good health, or at least avoiding disability or chronic pain, to be able to secure happiness, pleasure, or wellbeing in various ways, utilitarianism could also be seen as prioritizing major health improvements over certain other non-health harms or benefits.

[54] *See, e.g.*, Kristin Voigt, *Smoking and Social Justice*, 3 PUB. HEALTH ETHICS 91 (2010), https://academic.oup.com/phe/article-abstract/3/2/91/1456774 [https://perma.cc/46Y4-NWT7]; *see also* Bryan P. Thomas & Lawrence O. Gostin, *Tobacco Endgame Strategies: Challenges in Ethics and Law*, 22 TOBACCO CONTROl i55 (2013), https://pubmed.ncbi.nlm.nih.gov/23591513/ [https://perma.cc/C9N7-58N6]; Jessica Flanigan, *Double Standards and Arguments for Tobacco Regulation*, 42 J. MED. ETHICS 305

The preceding section discussed how FDA could evaluate PMTA and MRTP applications to see if it might be possible to develop corresponding AFPPH permissive final orders and, if so, how FDA could best approximate the first three of these ideal goals when developing the final orders, and then make a final determination as to whether issuing the final order was AFPPH (under FDA's ethically appropriate interpretation and application of the standard). To make any final orders found to be AFPPH even more ethically appropriate, FDA would then take advantage of any readily available means to modify the orders so they could approximate the remaining ethical ideals as closely as possible—to the extent that could be done without making them less AFPPH (i.e., without reducing the ability of the orders to satisfy the first three criteria as closely as possible).[55]

To start, FDA could identify the ethically relevant impacts that different possible PMTA or MRTP orders would or might produce through considering parallel or similar real world experiences and relevant available research and other information, with special attention not only to any impacts with public health consequences but also to any other major impacts that might affect personal autonomy, vulnerable or disadvantaged groups or related disparities and inequities, or might otherwise have any significant effects on the happiness or wellbeing of individual people. While doing all that might sound complicated or difficult, any expert consultations or elicitations or related modeling FDA did or secured to evaluate the potential net public health gains or harms from a possible order would likely include much of the information it would need to evaluate the order's health impacts on vulnerable or disadvantaged subpopulations and related inequitable health disparities. In addition, it should be relatively easy to identify the other major ethically relevant impacts or risks through reviewing available research on the impacts of product marketing and product claims, consultations with relevant experts, logic, and common sense—especially if FDA also set up related dockets to receive relevant public comments or if FDA issued its final

(2016), https://pubmed.ncbi.nlm.nih.gov/27048843/ [https://perma.cc/XQ3V-XYQG]; Lynn T. Kozlowski, *Younger Individuals and Their Human Right to Harm Reduction Information Should Be Considered in Determining Ethically Appropriate Public Health Actions,* NICOTINE & TOBACCO RES. (2019), https://pubmed.ncbi.nlm.nih.gov/30943281/ [https://perma.cc/SX4Y-589D]. *See generally, e.g.*, Ronald Bayer, *Stigma and the Ethics of Public Health: Not Can We but Should We*, 67 SOC. SCI. & MED. 463 (2008), https://www.sciencedirect.com/science/article/abs/pii/S0277953608001500?via%3Dihub [https://perma.cc/4VSN-MYWT]. For an ethical defense of tolerating stigma in some public health interventions, see Andrew Courtwright, *Stigmatization and Public Health Ethics*, 27 BIOETHICS 74 (2013), https://pubmed.ncbi.nlm.nih.gov/21797912/ [https://perma.cc/NF94-59S4].

[55] To ensure compliance with the not-arbitrary-or-capricious standard, FDA would, in addition, have to take advantage of any readily available reasonable steps to restructure or otherwise revise the rules to reduce the costs of the rule without reducing the likelihood or size of the net public health gains they would secure. *See supra* notes 23–24 and accompanying text. However, such costs are not likely ethically relevant, as they have no direct or significant discernable effect on the health or wellbeing of individual people or subpopulations. In particular, FDA's tobacco control activities, including any costs of issuing rules, are fully funded through established user fees already levied against the tobacco industry. TCA § 919, 21 U.S.C. § 387s (2018). Any lost government revenues would likely be small, especially if the new PMTA or MRTP products were taxed at rates comparable to those on the more-harmful products from which users might switch, and would be offset by the reduced government, private sector, and household expenditures and increased benefits caused by constructive switching to the new products that reduced user health harms, reduced disability, and increased worker productivity. *See, e.g.*, Bolger, *supra* note 1; *see also* Christine L. Baker et al., *Benefits of Quitting Smoking on Work Productivity and Activity Impairment in the United States, the European Union and China*, 71 INT'L J. CLINICAL PRAC. e12900 (2017), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5299499/ [https://perma.cc/ZD8U-EG8C].

permissive PMTA and MRTP orders only through a public notice-and-comment procedure.

Unlike with public health harms and the individual or subpopulation harms that underlie it, FDA would not need to estimate the likelihood or size of each of the other ethically relevant harms or risks caused by a possible order, nor would it be necessary to estimate the likelihood or size of the changes to those other ethically relevant impacts that different restrictions or requirements in the order might produce. All FDA would need to do would be to use similar, but less detailed, procedures to determine if there were readily available ways to modify the pending PMTA or MRTP order to reduce any of the identified ethical harms or risks caused by the order or to secure additional ethical gains—without significantly reducing the likelihood or size of the orders' potential net public health gains or increasing the likelihood or size of their possible net public health harms.[56]

To provide further clarification and detail, the next section of this paper explores how FDA might actually use the AFPPH standard, ethical goals, and related procedures that have been outlined here to require more helpful and complete applications for PMTA or MRTP orders for e-cigarettes, evaluate and process the applications, and then structure any possible permissive orders to produce the most likely and large net public health gains, with the smallest risks of producing net public health harms, and otherwise be as AFPPH and ethically appropriate as possible. It will then consider whether the final versions of the orders could be AFPPH, under either the most ethically appropriate AFPPH standard FDA might adopt and use or under any other legally viable refinement of the AFPPH standard. While other tobacco products have submitted and will be submitting PMTA and MRTP applications, such applications for e-cigarettes are not only likely to be much more numerous but will also raise more complex and challenging AFPPH and ethical issues than other non-smoked tobacco products given the recent surge of e-cigarette use among youth, including otherwise nonusers, and the ways e-cigarettes are more likely to delay or prevent total or smoking cessation.[57]

V. ETHICALLY APPROPRIATE FDA REQUIREMENTS FOR ALL PMTA OR MRTP APPLICATIONS FOR E-CIGARETTES

Following the preceding analysis, FDA would issue a formal guidance or perhaps a final rule explaining how it is interpreting and applying the AFPPH standard in the PMTA and MRTP context, and explaining what other steps it generally plans to take to ensure that any permissive PMTA or MRTP orders it issues are not arbitrary or capricious. To provide more specific guidance to manufacturers and importers of e-

[56] Given the overriding purpose of the TCA to protect the public health through reducing tobacco-related health harms and risks, and the absence of any competing TCA goals, it is likely that FDA would be violating the TCA and also be "arbitrary or capricious" if it revised a proposed rule to secure smaller net public health gains in order to reduce ethically relevant harms or increase other ethically relevant benefits, especially if they were non-health harms or benefits—even if an ethical analysis supported such changes. Accordingly, this analysis will not consider that type of situation.

[57] *See, e.g.*, *supra* note 17; *see also* Eric N. Lindblom, *Should FDA Try to Move Smokers to E-Cigarettes and Other Less-Harmful Tobacco Products and, If So, How?* 73 FOOD & DRUG L.J. 276–318 (2018) (regarding the ways e-cigarettes can both benefit and harm the public health).

cigarettes, those documents would also state that FDA has determined that it could not possibly make a determination that issuing a permissive PMTA or MRTP order for any specific e-cigarette might be AFPPH unless the application shows that the applicant has made a good faith effort to:

> (1) Take all available steps to make the e-cigarette as minimally harmful and risky as possible (without interfering with its ability to serve as an alternative way to inhale nicotine), including, but not necessarily limited to:
>
> - Minimizing contamination;
> - Eliminating any significant risk of exploding or burning users;
> - Preventing its use at temperatures higher than necessary to deliver nicotine as effectively as cigarettes (which can increase toxicity or deliver amounts of nicotine in excess of what smoking can deliver);[58]
> - Not using any additives unnecessary to delivering nicotine effectively for inhalation as a smoking substitute that are harmful or potentially harmful ingredients or might create harmful or potentially harmful constituents (HPHCs) during the e-cigarette's operation;[59]
> - Not using any ingredients or materials necessary for the operation of the e-cigarette that deliver significantly more harmful or potentially harmful constituents to users than

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[58] *See, e.g.*, Ariane Lechasseur et al., *Variations in Coil Temperature/Power and E-Liquid Constituents Change Size and Lung Deposition of Particles Emitted by an Electronic Cigarette*, 7 PHYSIOLOGICAL REP. e14093 (2019), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6540444/ [https://perma.cc/PMG4-ZSFJ]; *see also* Elise E. DeVito & Suchitra Krishnan-Sarin, *E-Cigarettes: Impact of E-Liquid Components and Device Characteristics on Nicotine Exposure*, 16 CURRENT NEUROPHARMACOLOGY 438 (2018), https://pubmed.ncbi.nlm.nih.gov/29046158/ [https://perma.cc/GVQ4-D6ZC]; Zachary T. Bitzer et al., *Effects of Solvent and Temperature on Free Radical Formation in Electronic Cigarette Aerosols*, 31 CHEMICAL RES. TOXICOLOGY 4 (2018), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6471512/ [https://perma.cc/3XNS-DJE5]. Federal law already requires e-cigarettes to have child-protective packaging. Child Nicotine Poisoning Prevention Act of 2015, Pub. L. No. 114-116, 130 Stat. 3 (2016) (codified at 15 U.S.C. § 1472a).

[59] The reference to HPHCs means to include any harmful or potentially harmful constituents, not just those on any existing FDA or other lists of HPHCs. *See, e.g.*, Harmful and Potentially Harmful Constituents in Tobacco Products and Tobacco Smoke: Established List, 77 Fed. Reg. 20,034 (Apr. 3, 2012). Banning all HPHC additives unnecessary to the e-cigarette's operation could make the product less attractive to smokers as a complete alternative (e.g., by banning added sweeteners or flavorings). But it appears that at least some added sweeteners and flavors would qualify as not being HPHCs. *See, e.g.*, Zachary T. Blitzer et al., *Effect of Flavoring Chemicals on Free Radical Formation in Electronic Cigarette Aerosols*, 120 FREE RADICAL BIOLOGY & MED. 72 (2018), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5940571/ [https://perma.cc/KVX2-2VY8]; *see also* My Hua, *Identification of Cytotoxic Flavor Chemicals in Top-Selling Electronic Cigarette Refill Fluids*, 9 SCI. REP. 2782 (2019), https://pubmed.ncbi.nlm.nih.gov/30808901/ [https://perma.cc/5VZC-D59T]. However, there is evidence that at least some e-cigarette menthol flavorings (often considered a necessary flavor for attracting menthol cigarette smokers) could be more risky than other added flavors. WH Lee, *Modeling Cardiovascular Risks of E-Cigarettes with Human-Induced Pluripotent Stem Cell–Derived Endothelial Cells*, 73 J. AM. C. CARDIOLOGY 2722 (2019), https://www.sciencedirect.com/science/article/abs/pii/S0735109719346960 [https://perma.cc/S7SU-7HW8].

other substitute ingredients or materials that would work just as well;[60] and

- Including any ingredients that would make using the e-cigarette less harmful or risky, if and when research identifies any such beneficial additives.[61]

(2) Provide reasonable estimates, based on available research and other evidence, of how harmful using the e-cigarette is compared to smoking (e.g., in terms of reduced risk of premature death, reduced-risk of major diseases) among new initiates, the harm reductions secured by smokers who switch completely to the e-cigarette, the impact on harms among smokers who switch to dual use, and the harm increases to former smokers who begin using the e-cigarette.

(3) Describe any new causes or types of health harms or risks caused by the use of the e-cigarette that are different from those from smoking.

(4) Provide a proposed final order that includes all available restrictions and requirements on the product's packaging, labeling, marketing, and sale that would prevent or reduce harm-increasing uses of the product without disproportionately reducing harm-reducing uses (i.e., reducing the expected net public health gains).

(5) Provide estimates of the likelihood and size of the different types of harm-reducing uses of the e-cigarettes that will or might occur in response to the proposed order being issued and the e-cigarette being marketed, such as smokers who would not otherwise quit switching to using only the e-cigarette and youth who would otherwise smoke initiating into using only the e-cigarette instead (and not moving on to smoking).

(6) Provide estimates of the likelihood and size of the different types of harm-increasing uses of the e-cigarettes that will or might occur in response to the proposed order being issued and the e-cigarette being marketed, such as initiation by youth or adults who would

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[60] For example, there is evidence that using certain metals in the heating elements of e-cigarettes produces more HPHCs than using other metals. Ahmad El-Hellani et al., *Carbon Monoxide and Small Hydrocarbon Emissions from Sub-Ohm Electronic Cigarettes*, 18 CHEMICAL RES. TOXICOLOGY 312 (2019), https://pubmed.ncbi.nlm.nih.gov/30656934/ [https://perma.cc/PFH7-3SEU]. There is also evidence that using vegetable glycerin instead of propylene glycol as the humectant in ENDS nicotine liquids might produce greater health harms and risks. Yeongkwon Son et al., *Hydroxyl Radicals in E-Cigarette Vapor and E-Vapor Oxidative Potentials under Different Vaping Patterns*, 32 CHEMICAL RES. TOXICOLOGY 1087 (2019), https://pubmed.ncbi.nlm.nih.gov/30977360/ [https://perma.cc/MX5W-66YL]. It is possible, however, that using a mixture of vegetable glycerin and propylene glycol produces a more cigarette-like throat hit, enabling the e-cigarette to serve as a more attractive smoking substitute. Arit Harvanko, *Stimulus Effects of Propylene Glycol and Vegetable Glycerin in Electronic Cigarette Liquids*, DRUG & ALCOHOL DEPENDENCE 326 (2019), https://pubmed.ncbi.nlm.nih.gov/30471584/ [https://perma.cc/8L5C-YPMV]. More generally, *see* Alexandra M. Ward et al., *Electronic Nicotine Delivery System Design and Aerosol Toxicants: A Systematic Review*, PLOSONE (2020), https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0234189 [https://perma.cc/7MNG-YXD3].

[61] *See* Qi Zhang et al., *Optimized Bexarotene Aerosol Formulation Inhibits Major Subtypes of Lung Cancer in Mice*, 19 NANO LETTERS 2231 (2019), https://pubmed.ncbi.nlm.nih.gov/30873838/ [https://perma.cc/Y29Q-TBUG] (describing an interesting future possibility).

otherwise not use any tobacco-nicotine product (and some possibly moving on to smoking), smokers switching or engaging in dual use instead of quitting all use or quitting smoking, and former smokers using the e-cigarette who would not otherwise relapse into using any tobacco-nicotine product.

(7) Provide estimates of the likelihood and size of the public health impacts (e.g., in life years or QALYs) from the different possible harm-reducing uses and the different harm-increasing uses of the e-cigarette (e.g., over the next ten, twenty-five, and fifty years)—and show that the former are, in absolute terms, larger than the latter, even when the most conservative or pessimistic reasonable assumptions and estimates are used.[62]

(8) Show that issuing the order is clearly more likely to produce a net public health gain than a net public health loss and the overall probable gain (likelihood times size) is larger than the overall possible loss (likelihood times size).

To help ensure that any final order would also be not arbitrary or capricious (and as ethically appropriate as possible within the constraints of the TCA and other laws), FDA would also require PMTA and MRTP applications to show that the applicant had made a good faith effort to:

(9) Design and test any variable characteristics of the product, its packaging and labeling, and any included instructions for use or other materials to ensure that they do not mislead smokers or other consumers in any potentially harmful ways and that any provided information is accessible and understandable to persons with less education or lower literacy or for whom English is not a primary language.

(10) Estimate the impact of the proposed final order and the marketing of the e-cigarette on key vulnerable and disadvantaged subpopulations—such as youth, less-educated or lower-income persons, racial or ethnic minorities, or persons suffering from mental illness or substance abuse—and determine whether there are other available ways to structure the product, its packaging or labeling, or the proposed order so that comparable net public health gains could be secured with less likely and smaller new harms to the vulnerable and disadvantaged subpopulations and by having

[62] To support and standardize such projections, and facilitate FDA's subsequent review and evaluation of the applicant's estimates, FDA could provide applicants with a basic model setting forth the baseline data and projections into the future in terms of numbers of smokers, e-cigarette users, etc. and related numbers of deaths (lost life years of QALYs), broken down by key subpopulations, and applicants could show how they estimate that baseline situation would change over time based on their worst-case, best-case, and most-likely-case estimates of the effect of the marketing of their e-cigarette, pursuant to their proposed final order, on initiation, smoking cessation, total cessation, dual use, relapse, etc.

> either less-negative or more-positive possible impacts on related health disparities.[63]

FDA would reject any PMTA or MRTP application that did not provide all of this necessary information and required estimates unless FDA determined that if the applicant made requested changes to the product or its packaging and labeling or if FDA revised the proposed final order it could issue an ethically AFPPH permissive final order that would enable FDA to secure more rapid and larger public health gains than it could otherwise secure.

Once FDA had a non-rejected application with an e-cigarette that complied with all the above-described harm-minimizing requirements, FDA would need to use the information provided in the application, other available relevant research and information, and its own expert consultations or elicitation procedures or other reasonable means to develop its own estimates of how harmful using the e-cigarette would be compared to smoking and whether smokers who quit completely would secure significant health harm and risk reductions. If FDA's reasonable worst-case estimates indicated that switching smokers would not secure significant harm-reduction benefits or, when substituted for the applicant's larger harm-reduction estimates, would no longer support the applicant's estimates of likely future net public health gains, FDA would reject the application.

Otherwise FDA would use its harm-reduction estimates to guide its evaluation of the product's characteristics and the proposed final order and possible improvements to them. The more harmful FDA determined using the e-cigarette might be, the more its public-health-maximizing calculus would favor preventing harm-increasing uses over encouraging harm-reducing uses. For example, if using the e-cigarettes were estimated to be no more than 10% as harmful as smoking, FDA would be able to accept considerably more nonuser initiation by youth and adults, and more former smoker relapse into e-cigarette use, for each smoker who switched completely, compared to if the e-cigarette were estimated to be as much as 60% as harmful.[64]

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[63] Although they make references to PMTA applications including information about possible harms and risks and benefits from the marketing of the subject product and possibly including some restrictions or requirements in proposed final orders, FDA's Proposed Rule for PMTA applications and final PMTA Guidance for e-cigarettes do not require or suggest that applicants provide the information or estimates described here. *See supra* note 48 and accompanying text.

[64] How strongly FDA might prioritize preventing harm-increasing uses over encouraging harm-reducing users, or vice versa, would also need to consider the fact that smokers who switched completely to a 10% or 60% as harmful e-cigarette would not secure a 90% or 40% reduction in their tobacco-related harms and risks because of the harms already caused by their prior smoking. Looking just at reduced-risk of death, smokers over the age of fifty-five who quit all use likely reduce their risk of smoking-caused death by only about 50% or somewhat less. Using those same ratios, smokers switching to a 10% as harmful e-cigarette would reduce their risks by roughly 42%, while switching to a 60% as harmful e-cigarette would reduce harms by only about 16%. Michael J. Thun et al., *50-Year Trends in Smoking-Related Mortality in the United States*, 368 NEW ENG. J. MED. 351 (2013), https://pubmed.ncbi.nlm.nih.gov/23343064/ [https://perma.cc/3TXG-BJVR]. However, such linear, partial harm reductions from replacing smoking with harmful e-cigarette use, instead of quitting all harmful use, would be highly unlikely. Because new harms to the body would not be eliminated, and because e-cigarettes could harm the body in different ways than smoking, the actual harm-reduction percentages from switching would be somewhat lower. *See, e.g.*, Nat'l Academies of Sci., Eng'g, and Med., *Public Health Consequences of E-Cigarettes* 72 (2018), https://pubmed.ncbi.nlm.nih.gov/29894118/ [https://perma.cc/R66C-Q4A7]; Choon-Young Kim et al., *Dual Use of Electronic and Conventional Cigarettes Is Associated With Higher Cardiovascular Risk Factors in Korean Men*, 10 SCI. REPORTS 5612 (2020), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7101350 [https://perma.cc/K749-3A52]; *see also* Albert D. Osei et al., *The Association Between E-*

VI. ETHICALLY APPROPRIATE FDA REQUIREMENTS AND RESTRICTIONS TO INCLUDE IN ALL PERMISSIVE PMTA OR MRTP ORDERS FOR E-CIGARETTES

Establishing the following restrictions and requirements would reduce harm-increasing uses of PMTA or MRTP e-cigarettes. They would also do so without disproportionately discouraging constructive switching from smoking, unless FDA determines that the health harms and risks from the subject e-cigarettes were quite small compared to smoking. Even with a quite low relative risk, these restrictions and requirements could still reduce harm-increasing uses without disproportionately discouraging harm-reducing uses because they include measures that would work directly to help encourage smokers who would not otherwise quit to switch completely to using the e-cigarettes. E-cigarettes receiving MRTP orders could also effectively attract and keep smokers with their permitted reduced-risk or reduced-exposure claims.[65] In addition, any impact these restrictions and requirements had on making smokers less likely to try or become regular users of the e-cigarette would be irrelevant if FDA were able to take other actions to prompt smokers to switch (or quit all use) and were not forced to follow a tobacco control policy of relying primarily on e-cigarettes being able to attract smokers to switch.

Indeed, FDA would need to consider the existing regulatory context and what other tobacco control actions the agency, or others, would be taking in the near future to determine which of the following restrictions and requirements, or other possibilities, would work effectively to secure larger and more likely net public health gains by reducing harm-increasing uses without disproportionately discouraging harm-reducing uses. For example, if FDA were able to issue a strong new anti-smoking rule (e.g., to ban all added flavors or minimize nicotine levels in all smoked tobacco products), that would push many smokers to quit or switch to e-cigarettes. As a result, FDA would not need to rely as much, or at all, on e-cigarettes being able to attract

Cigarette Use and Cardiovascular Disease Among Never and Current Combustible Cigarette Smokers: BRFSS 2016 & 2017, 132 AM. J. MED. 949 (2019), https://pubmed.ncbi.nlm.nih.gov/30853474/ [https://perma.cc/UQ8W-FMBB].

[65] A basic assumption underlying these restrictions and requirements—supported by available research—is that smokers will be attracted to the e-cigarettes and likely to stick with them if they believe doing so will significantly reduce their health harms and risks and the e-cigarettes deliver nicotine into the lungs in a sufficiently effective way, even if the e-cigarettes and their packaging and labeling are not otherwise especially attractive. But nonsmokers will be much less likely to try e-cigarettes if the product and its packaging and labeling do not have various attractive features (other than offering a product less harmful than smoking). *See, e.g.*, Kim A.G.J. Romijnders et al., *Perceptions and Reasons Regarding E-Cigarette Use among Users and Non-Users: A Narrative Literature Review*, 15 INT'L J. ENVT'L. RES. & PUB. HEALTH 1190 (2018), https://pubmed.ncbi.nlm.nih.gov/29882828/ [https://perma.cc/UN3N-F7ZY]; *see also* Alexander Persoskie et al., *Perceived Relative Harm of Using E-Cigarettes Predicts Future Product Switching Among US Adult Cigarette and E-Cigarette Dual Users*, 114 ADDICTION 2197 (2019), https://pubmed.ncbi.nlm.nih.gov/31278802/ [https://perma.cc/4QSU-AXN6]; Samane Zare et al., *A Systematic Review of Consumer Preference for E-Cigarette Attributes: Flavor, Nicotine Strength, and Type*, 13 PLOS ONE e0194145 (2018), https://pubmed.ncbi.nlm.nih.gov/29543907/ [https://perma.cc/XL6XR95H]; Cosima Hoetger et al., *Influence of Electronic Cigarette Characteristics on Susceptibility, Perceptions, and Abuse Liability Indices Among Combustible Tobacco Cigarette Smokers and Non-Smokers*, 16 INT'L J. ENVT'L RES. & PUBLIC HEALTH E1825 (2019), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6572235 [https://perma.cc/3RKY-P62N].

smokers to switch (e.g., through flavorings or sweeteners, reduced-risk claims, or attractive packaging or product characteristics), which would also attract youth and other nonusers. Or if many states followed the lead of Massachusetts and banned all flavored tobacco products, whether or not FDA's permissive PMTA or MRTP orders restricted flavors in e-cigarettes could become largely moot.[66] Similarly, a new federal law raising the federal minimum age for tobacco product sales from 18 to 21 could reduce the risk that youth would be able to purchase or otherwise obtain any e-cigarettes receiving permissive PMTA or MRTP orders (or obtain smoked tobacco products instead).[67]

If FDA's own expert analyses determined that some or all of these restrictions and requirements were necessary to make allowing any e-cigarette on the market AFPPH, it could establish them through issuing a binding final rule (if allowed to do so). Otherwise, FDA could publicize them as possible measures that applicants could include in proposed final PMTA or MRTP orders to regulate future packaging and labeling changes, marketing, and sales in order to increase the chances that FDA would be able to find issuing a permissive order AFPPH.[68] Either way, to maintain flexibility and allow for potentially more effective new approaches, FDA would also enable applicants to secure exemptions to these restrictions and requirements by providing convincing evidence in their applications or after any final orders were issued that the exceptions would secure additional net public health gains by prompting increases in harm-reducing users that would more than offset any related increases to harm-increasing uses.[69]

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[66] Mass. Gen. Laws ch. 270, § 28 (2020).

[67] Jennifer Maloney & Alex Leary, *Trump Supports Raising E-Cigarette Purchase Age to 21*, WALL ST. J. (Nov. 8, 2019), https://www.wsj.com/articles/trump-supports-raising-e-cigarette-purchase-age-to-21-11573239251 [https://perma.cc/39LG-4HBC].

[68] Under the TCA, any tobacco product, including products allowed on the market with PMTA or MRTP orders, may not be marketed with any substantial changes to its characteristics unless the manufacturer first obtains another permissive PMTA or substantial equivalence new product order from FDA. *See generally* TCA § 910, 21 U.S.C. § 321j (2018). Pursuant to a D.C. Circuit Court ruling, however, it appears that substantial changes to an existing product's labeling or packaging would not trigger that requirement to obtain a permissive new product order from FDA, even if the labeling or packaging changes would increase public health risks and harms. Philip Morris Inc. v. FDA, 202 F. Supp. 3d 31, 48–54 (D.C. Cir. 2016). Accordingly, FDA cannot rely on the TCA's new product provisions to prevent applicants receiving permissive PMTA or MRTP orders from changing the product's packaging and labeling in ways that are not AFPPH.

[69] E-cigarettes receiving a permissive PMTA or MRTP order including all restrictions and requirements that would discourage harm-increasing uses without disproportionately discouraging harm-reducing uses would be at an enormous competitive disadvantage compared to any e-cigarettes allowed to be marketed without complying with them. The assumption here is that once FDA issued any final permissive PMTA or MRTP order, it would aggressively enforce against any e-cigarettes on the U.S. market without a permissive PMTA order if they did not quickly begin complying with the same restriction and requirements—regardless of what enforcement policies FDA might have previously been operating under to tolerate their marketing despite their illegality. This problem could, at some point, disappear as all e-cigarettes currently on the market without permissive PMTA orders must, by court order, submit a PMTA application by September 9, 2020 or be subject to immediate removal, with FDA generally required to make a final decision on the application within one year. *Coronavirus (COVID-19) Update: Court Grants FDA's Request for Extension of Premarket Review Submission Deadline for Certain Tobacco Products Because of Impacts from COVID-19*, FOOD & DRUG ADMIN. (2020), https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-court-grants-fdas-request-extension-premarket-review-submission-deadline [https://perma.cc/WQ23-EY5Y]; Am. Acad. of Pediatrics v. FDA, 379 F. Supp. 3d 461 (D. Md. 2019), enforced 399 F. Supp. 3d at 487; appeals rejected or dismissed in In re Cigar Ass'n of Am., 2020 WL 2116554 (4th Cir. May 4, 2020). Regardless of these court deadlines issued in a different context, once

As a preliminary matter, if FDA determined that issuing a permissive PMTA or MRTP order for any e-cigarettes would be ethically AFPPH, FDA should allow the e-cigarettes on the market for use only as a complete substitute for smoking, as the only way that e-cigarettes can work effectively to produce public health gains is when they are used as a complete substitute for regular smoking. Allowing them on the market for this specific purpose would not only highlight their limited beneficial purposes but also help to emphasize that any other use of the e-cigarette will increase user health harms and risks.[70] It would also make it much easier for FDA to ensure that any restrictions or requirements placed on the packaging labeling, advertising, or other promotion of the e-cigarettes were consistent with First Amendment constraints, as the manufacturers and other sellers of the e-cigarettes would have First Amendment rights to communicate with only their intended, FDA-authorized customers: smokers and former smokers who had switched.[71]

A. Additional Product, Packaging, and Labeling Restrictions and Requirements

(1) Require that the e-cigarette itself and its packaging and labeling are plain and drab, with a dull standardized color, without any product materials or components unnecessary for the e-cigarette's operation (or to reduce harms and risks), without any unnecessary packaging flourishes, and without any images, shapes, or text on

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FDA issues a permissive PMTA order placing various restrictions and requirements on an e-cigarette to allow it to be legally marketed, FDA would likely be found arbitrary or capricious, and perhaps in violation of the AFPPH standard and other legal requirements, if it did not begin enforcing against any e-cigarettes still illegally on the market without a permissive PMTA order that do not also comply with the requirements and restrictions in the PMTA order (as that would be treating illegal e-cigarettes more favorably than legal ones).

[70] Using e-cigarettes to reduce but not replace smoking is unlikely to secure any significant harm reductions given that smoking harms and risks are not significantly reduced without sharp consumption reductions to extremely low levels. *See, e.g.*, Rachna Begh et al., *Does Reduced Smoking if You Can't Stop Make Any Difference?,* 13 BIOMED CENT. MED. 257 (2015), https://pubmed.ncbi.nlm.nih.gov/26456865/ [https://perma.cc/93VD-UC5V]; *see also* Peter N. Lee, *The Effect of Reducing the Number of Cigarettes Smoked on Risk of Lung Cancer, COPD, Cardiovascular Disease and FEV(1)—A Review*, 67 REG. TOXICOLOGY & PHARMACOLOGY 372 (2013), https://pubmed.ncbi.nlm.nih.gov/24013038/ [https://perma.cc/UW6Y-7Z5V]; Allan Hackshaw et al., *Low Cigarette Consumption and Risk of Coronary Heart Disease and Stroke: Meta-Analysis of 141 Cohort Studies in 55 Study Reports*, 360 BRITISH MED. J. j5855 (2018), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5781309/ [https://perma.cc/9LLM-NPT9]; Bill Poland & Florian Teischinger, *Population Modeling of Modified Risk Tobacco Products Accounting for Smoking Reduction and Gradual Transitions of Relative Risk*, 19 NICOTINE & TOBACCO RES. 1277 (2017), https://pubmed.ncbi.nlm.nih.gov/28371856/ [https://perma.cc/B3JF-UQD3]. In addition, the e-cigarette use allowing for such smoking reductions would create new harms and risks, possibly including new health risks and harms from combining smoking and using the e-cigarette. *See, e.g.*, Nat'l Academies of Sci., Eng'g, and Med., *supra* note 64, at 72; Kim et al., *supra* note 64; *see also* Osei et al., *supra* note 64. Moreover, any harm-reductions that might possibly be secured when e-cigarette use enables smokers to reduce their smoking to extremely low levels would likely occur as a transition to complete switching (not as a sustained smoking-reduction, harm-reduction strategy or pattern). On the other hand, allowing e-cigarettes to be inaccurately perceived as an effective way to reduce harms by reducing but not replacing smoking would likely prompt more smokers to engage in neutral or harm-increasing dual use instead of switching completely.

[71] *See e.g.*, Lorillard Tobacco Co. v. Reilly, 533 U.S. 525, 571 (2001); *see also* Cent. Hudson Gas & Elec. Corp. v. Pub. Serv. Comm'n of N.Y., 447 U.S. 557, 564 (1980); Eric N. Lindblom, *Effectively Regulating E-Cigarettes and Their Advertising—And the First Amendment*, 70 FOOD & DRUG L.J. 57 (2015).

the product, packaging, or label (except for any legally required text or images) other than the product's name in black text in a limited size.[72]

(2) Prohibit any additives unnecessary to delivering nicotine effectively for inhalation as a smoking substitute, such as added vitamins or supplements, that could mislead consumers about product harms and risks, the purpose of the e-cigarette, or user benefits.

(3) Prohibit added flavors, other than tobacco-flavor, with, at most, only very carefully chosen and structured additional exceptions.

Some supporters of e-cigarette harm-reduction believe that added flavors, beyond tobacco, are necessary in the existing regulatory environment to encourage smokers to switch or, perhaps even more, to keep former smokers who begin using e-cigarettes from switching back.[73] So far, however, e-cigarette flavors appear to have worked much more powerfully in the U.S. to increase youth initiation than to encourage or sustain complete smoker switching.[74] E-cigarette flavors would also be less necessary to encourage or maintain smoker switching if FDA banned all added flavors in smoked tobacco products or took other actions to make smoking less attractive or to inform smokers of the harm reductions available from switching if they do not quit.[75] It is also

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[72] *See, e.g.*, Ann McNeill et al., *Tobacco Packaging Design for Reducing Tobacco Use*, 4 COCHRANE LIB. (2017), https://pubmed.ncbi.nlm.nih.gov/28447363/ [https://perma.cc/LXR7-D4PJ]; *see also* Nicole Hughes et al., *Perceptions and Impact of Plain Packaging of Tobacco Products in Low and Middle Income Countries, Middle to Upper Income Countries and Low-Income Settings in High-Income Countries: A Systematic Review of the Literature*, 6 BMJ OPEN (2016), https://pubmed.ncbi.nlm.nih.gov/27000787/ [https://perma.cc/9LVC-Z8FY]; Lauren K. Lempert & Stanton Glantz, *Packaging Colour Research by Tobacco Companies: The Pack as a Product Characteristic*, 26 TOBACCO CONTROL 307 (2017), https://pubmed.ncbi.nlm.nih.gov/27255118/ [https://perma.cc/87R2-LM3E].

[73] *See, e.g.*, Guy Bentley, *The Public Health Case for E-Cigarette Flavors*, REASON FOUNDATION (Oct. 18, 2019), https://reason.org/commentary/the-public-health-case-for-e-cigarette-flavors/ [https://perma.cc/V99C-ZT35].

[74] *See, e.g.*, Samir S. Soneji et al., *Use of Flavored E-Cigarettes Among Adolescents, Young Adults, and Older Adults: Findings From the Population Assessment for Tobacco and Health Study*, 134 PUB. HEALTH REP. 282 (2019), https://pubmed.ncbi.nlm.nih.gov/30857471/ [https://perma.cc/H9T6-VRAN]; *see also* Liane M. Schneller et al., *Use of Flavored E-cigarettes and the Type of E-Cigarette Devices Used Among Adults and Youth in the US—Results from Wave 3 of the Population Assessment of Tobacco and Health Study (2015–2016)*, 16 INT'L J. ENVT'L. RES. PUB. & HEALTH E2991 (2019), https://pubmed.ncbi.nlm.nih.gov/31434229/ [https://perma.cc/8ERS-56VA]; Robin Landry et al., *The Role of Flavors in Vaping Initiation and Satisfaction Among U.S. Adults*, 99 ADDICTIVE BEHAVIOR 106077 (2019), https://pubmed.ncbi.nlm.nih.gov/31437770/ [https://perma.cc/KC44-DE5U]; Zare et al., *supra* note 65. It is possible, however, that the surge in youth e-cigarette use in the United States would have largely occurred even if flavors had been strictly limited, prompted primarily by the emergence of Juul e-cigarettes—with their sharply different high-tech appearance and more powerful nicotine delivery—and their aggressive social media marketing. *See, e.g.*, FOOD & DRUG ADMIN., *2018 NYTS Data: A Startling Rise in Youth E-Cigarette Use* (Feb. 6, 2019), https://www.fda.gov/tobacco-products/youth-and-tobacco/2018-nyts-data-startling-rise-youth-e-cigarette-use [https://perma.cc/6DTZ-4FCJ]. It is also possible, for the same reasons, that Juul's marketing would also have also been similarly successful at attracting adult and youth smokers if flavors had been strictly limited beforehand.

[75] Currently, cigarettes are allowed to have a characterizing flavor of only tobacco or menthol, but there are no restrictions on flavors for any other smoked (or other) tobacco products. TCA § 907(a)(1)(A), 21 U.S.C. § 387g(a)(1)(A) (2018). Even if prevented from directly banning all or most added flavors in smoked tobacco products, FDA could still take enforcement action to ensure that all cigarettes, including those labeled as "little cigars" or "filtered cigars," are complying with the existing flavor restrictions. *See,*

possible that an MRTP e-cigarette allowed to be marketed with claims of reduced-risk compared to smoking would not also need additional flavors to attract smokers and keep them from switching back (especially if FDA took action to prevent any other e-cigarettes without required PMTA orders from being sold with added flavors other than tobacco). In addition, as noted above, applicants would be allowed to have certain flavors, besides tobacco, if they provided convincing evidence that they would help to secure larger net public health gains. However, if FDA determined that, given existing regulatory realities, it was possible that allowing PMTA or MRTP e-cigarettes to have additional flavors besides tobacco might make larger net public health gains more likely under certain conditions (e.g., only also allow menthol or a small, limited number of straight-forward additional basic flavors, with no creative naming, and with the flavored e-cigarettes sold only in adult-only stores), FDA could make that the minimum standard for applications. But applicants could still submit evidence to support allowing additional flavors or different flavor-related marketing restrictions, and FDA could ultimately include different or more strict flavor regulations in any final permissive PMTA or MRTP orders it issued if it determined that would be AFPPH.

> (4) Require warning labels and package inserts (developed by FDA) to inform consumers that the e-cigarette is intended only for use as a complete substitute for smoking and any other use will increase health harms and risks to users, with the inserts also stating that total cessation or never starting is the most effective way to minimize health harms and providing information on where those desiring more information about how to quit all use can obtain it.[76]

These required warnings and inserts would be developed by FDA, based on available research, and tested to ensure that they would work as effectively as possible to deliver this information in an accurate, not misleading way to smokers (and others who might see the warnings or inserts). They would also be designed to be understandable by those with lower literacy or with English not their primary language, and they would be designed to ensure that they do not stigmatize smokers or e-cigarette users. In this way, FDA would be ensuring that the warnings and inserts would work as effectively as possible to encourage harm-reducing uses of the e-cigarette and discourage harm-increasing uses while also being ethically appropriate and compliant with the First Amendment.[77]

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e.g., Eric N. Lindblom et al., *Has FDA Abandoned Its Efforts to Make Fake-Cigar Cigarettes Comply with Federal Tobacco Control Laws That Apply to Cigarettes But Not Cigars?*, TOBACCO CONTROL (2020), https://tobaccocontrol.bmj.com/content/early/2020/02/23/tobaccocontrol-2019-055395.full?ijkey=305cC2IPMnUJcnW&keytype=ref [https://perma.cc/GWF8-H3JL].

[76] *See, e.g.*, Eric N. Lindblom et al., *FDA-Required Tobacco Product Inserts & Onserts—And the First Amendment,* 72 FOOD & DRUG L.J. 25 (2017); *see also* Tobacco Products; Required Warnings for Cigarette Packages and Advertisements*,* 84 Fed. Reg. 42,754 (proposed Aug. 16, 2019); Lauren K. Lempert & Stanton Glantz, *Implications of Tobacco Industry Research on Packaging Colors for Designing Health Warning Labels*, 18 NICOTINE & TOBACCO RES. 1910 (2016), https://pubmed.ncbi.nlm.nih.gov/27146637/ [https://perma.cc/5TRQ-AQFS].

[77] Besides avoiding ethically inappropriate stigmatizing of addicted smokers or e-cigarette users and being designed not to increase inequitable health disparities, such warnings and inserts would respect personal autonomy by providing relevant information smokers and others need to make independent, informed decisions. To ensure further that the required warnings and inserts would not raise any significant

To further protect against youth use, FDA could also do the following:

(5) Require e-cigarettes to include available biometric and other technologies that would prevent their use by anyone other than their age-and-ID-verified buyers (thereby preventing subsequent distributions or sales to youth) and prevent their use in certain inappropriate locations, such as schools or other areas where youth congregate.[78]

B. Advertising Restrictions and Requirements

Beyond requiring effective warnings and information with any permitted cigarette advertising, FDA could also place the following restrictions and requirements on e-cigarette advertising:

(1) Allow online or electronic advertising or sales of the e-cigarettes only with effective prior age and ID verification (paralleling what FDA included in the permissive PMTA order it issued for the Philip Morris "heat not burn" inhalable IQOS tobacco products).[79]
(2) Prohibit the e-cigarettes from being displayed or advertised in youth-accessible brick and mortar retail outlets, but allow text-only signage that states that the e-cigarettes are available for sale, lists prices, and offers to provide additional information about the e-cigarettes for verified adults who request it.
(3) Prohibit any other advertising of the e-cigarettes except in adult-only stores and through direct communications to pre-verified adults, such as e-mail, social media, direct mail, or in-person communications.
(4) Require permitted advertising to include a warning or statement that the e-cigarette is intended only for use as a complete substitute for smoking and any other use will increase health harms and risks to users, and offer a website address (to an FDA-created website)

First Amendment concerns, FDA could design them to identify FDA (as opposed to the manufacturer) as their author or source and avoid any content that could be characterized as urging the intended users not to use the product (by quitting all use instead), especially through emotional manipulation. *See, e.g.*, Lindblom et al., *FDA-Required Tobacco Product Inserts & Onserts—And the First Amendment*, 72 FOOD & DRUG L.J. 25 (2017).

78 *See, e.g.*, Annie Palmer, *Juul Reveals Plans for Smart Bluetooth E-Cigs Than Use Biometric Data to Prove a Smoker's Age and Won't Work Near Schools*, DAILY MAIL (Aug. 2, 2018), https://www.dailymail.co.uk/sciencetech/article-6021125/Juul-reveals-plans-smart-Bluetooth-e-cigs-use-biometric-data-prove-smokers-age.html [https://perma.cc/5AU9-GRVP]. But FDA would also need to put measures in place to prevent manufacturers from using the technologies to collect data on their customers' use of the e-cigarette and use it to promote harm-increasing use.

79 IQOS Final PMTA Order, *supra* note 30; *see also* Prevent All Cigarette Trafficking Act of 2009, Pub. L. No. 111-154, 124 Stat. 1087 (2010). Ideally, FDA would issue a rule to apply these restrictions to all tobacco products, as the youth-protecting justifications for applying them to IQOS fully support applying them more broadly. IQOS PMTA Decision Summary, *supra* note 31, at app. Going further, FDA could also require all such advertising to offer recipients an opt-out option to stop all future communications, and the PMTA or MRTP final orders could require that any such online or electronic advertising or sales of the e-cigarettes also require potential recipients or buyers to self-identify as smokers or former smokers now using e-cigarettes (the only persons who could use the e-cigarettes to reduce harms).

> where consumers can obtain more information about the product, its harm-increasing and harm-reducing uses, and other options for reducing health harms and risks.[80]

To include these restrictions and requirements in a final permissive PMTA or MRTP order, FDA would have to determine, with a reasonable underlying explanation, that they were necessary to make the order AFPPH (i.e., by reducing the likelihood and size of the possible health harms from the product's marketing under the order without disproportionately reducing the likelihood or size of the possible health gains). Doing that should also ensure that the requirements and restrictions on the product's labeling, advertising, or other corporate speech would be acceptable under the First Amendment as the least-restrictive means of securing a substantial government interest (protecting the public health).[81] In addition, these restrictions and requirements would leave manufacturers and other sellers of the e-cigarettes with reasonable ways to communicate relevant product information to the product's intended and authorized consumers (adult smokers or former smokers now using e-cigarettes), thereby further diminishing any First Amendment concerns.[82] As noted above, FDA would have further ensured First Amendment compliance by designing and testing any required warnings, labeling, or product inserts to make sure that they were accurate and not misleading, clearly from FDA and not the manufacturers, and would effectively convey relevant, useful information (rather than manipulate consumers or actively discourage legal, authorized sales and use of the product).

These efforts by FDA—along with its testing of the communications to ensure they did not stigmatize smokers or e-cigarette users and would be accessible to less-educated or less-English-literate consumers—would also ensure that the labeling and advertising restrictions and requirements were ethically appropriate. More generally, all of the restrictions or requirements, given their purpose and reasonably determined impacts, would be ethically desirable as reducing any public health risks or subpopulation or individual health harms or risks created by allowing the marketing of the e-cigarette, and they do not appear to raise any other new ethically relevant concerns that could possibly offset those ethical gains. Because of their broad application to benefit a smoking population that disproportionately consists of persons with less education, lower incomes, and higher levels of mental illness and substance abuse disorders,[83] the restrictions and requirements do not suggest any risk of disproportionately harming vulnerable or disadvantaged subpopulations or otherwise increasing inequitable health disparities. Any permissive PMTA or MRTP order

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[80] *See supra* notes 76–77 and accompanying text.

[81] *See e.g.*, Lorillard Tobacco Co. v. Reilly, 533 U.S. 525 (2001); *see also* Disc. Tobacco City & Lottery, Inc. v. United States, 674 F.3d 509, 531–37 (6th Cir. 2012) (upholding the MRTP pre-market order process, as described in the TCA, against tobacco industry First Amendment challenges). If the courts could strike down a commercial speech restriction or requirement that FDA had reasonably determined was necessary to include in the PMTA order to enable FDA to find that issuing it was AFPPH, FDA would have to withdraw the PMTA order as no longer AFPPH, preventing any marketing of the subject product, despite its ability to secure public health gains with the speech constraints—which would contradict both the TCA's goal of protecting the public health and the purpose of First Amendment protections.

[82] *See supra* note 71 and accompanying text.

[83] *See, e.g.*, Jeffrey Drope et al., *Who's Still Smoking? Disparities in Adult Cigarette Smoking Prevalence in the United States*, 68 CA: CANCER J. FOR CLINICIANS 106 (2018), https://pubmed.ncbi.nlm.nih.gov/29384589/ [https://perma.cc/M73C-DTT7].

would also be directly increasing individual choice by allowing new products to enter the market legally or directly supporting informed, autonomous decision making by allowing tobacco products to be marketed with accurate and not-misleading reduced-risk or reduced-exposure claims. That eliminates any possible ethical significance of any perceived personal autonomy infringements by the above restrictions blocking certain flavorings or otherwise limiting certain product characteristics, as FDA could not issue the permissive PMTA or MRTP orders as ethically AFPPH, and provide those larger personal autonomy gains, without those restrictions.[84] Similarly, it is difficult to imagine any possible individual declines in wellbeing or happiness caused by all these restrictions or requirements that would not be fully justified by the expected public health gains from issuing the permissive order, even under a utilitarian analysis that did not favor public health or individual health gains over other forms of increasing overall wellbeing or happiness.

C. Additional Refinements to the Possible Permissive Orders and Final Evaluations

Once FDA had included in the draft permissive order all of the above restrictions and requirements that would reduce the health harms and risks from issuing the order without disproportionately reducing harm-reducing uses of the e-cigarette, FDA would develop or secure its own expert estimates of the overall likelihood and size that issuing the permissive order would secure a net public health gain versus the likelihood and size that it would secure a negative net public health impact instead. To further refine and improve the draft order, FDA would then seek comments from relevant experts and other interested parties, perhaps through a formal notice-and-comment process on: a) how the order might be improved to further reduce the risk of harms from harm-increasing uses of the e-cigarette, without disproportionately shrinking harm-reducing uses; and b) whether FDA's estimated likelihood and size of the expected net public health gains were large enough compared to the likelihood and size of a possible negative net public health impact to make issuing the order AFPPH.

In response to these comments, FDA would improve the draft permissive order, much as it would improve a proposed rule through notice-and-comment rulemaking, before making its final evaluation as to whether issuing the permissive final order would be AFPPH. As previously discussed, determining that it would not be AFPPH to issue the permissive order would be fairly straight forward if the most conservative reasonable estimates of the likelihood and size of the net public health gains were smaller than or not clearly significantly larger than the worst-case reasonable estimates of the likelihood and size of the possible net public health harms. But making a decision that issuing the proposed order would be AFPPH might be much more

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[84] *See* Eric N. Lindblom, *Are There Any Ethical Barriers to Effective Antismoking Measures?*, 107 AM. J. PUB. HEALTH 1364 (2017), https://ajph.aphapublications.org/doi/abs/10.2105/AJPH.2017.303978 [https://perma.cc/3CVE-4VT8] (providing a more comprehensive discussion of personal autonomy concerns and their ultimate irrelevance to tobacco control regulations and policymaking); *see also* Lindblom, *supra* note 39. *But see* Flanigan, *supra* note 54. *See generally* Larry O. Gostin & Kieran G. Gostin, *A Broader Liberty: J.S. Mill, Paternalism and the Public's Health*, 123 PUB. HEALTH 214 (2009), https://pubmed.ncbi.nlm.nih.gov/19249800/ [https://perma.cc/4DC8-QGH9]; James Wilson, *Why It's Time to Stop Worrying About Paternalism in Health Policy*, 4 PUB. HEALTH ETHICS 269 (2011), https://academic.oup.com/phe/article-abstract/4/3/269/1501732 [https://perma.cc/MJW6-W3S8]; Alec Rajczi, *Liberalism and Public Health Ethics*, 30 BIOETHICS 96 (2016), https://pubmed.ncbi.nlm.nih.gov/25960065/ [https://perma.cc/U6W7-8PHW].

difficult, unless these expert estimates showed that the conservative estimates of the probable net public health gains were considerable and much more likely than any possible net public health harm and the size of any possible net public health harms were, at worst, still quite small.

With luck, following the procedures here would produce such estimates and simplify FDA's decision making. In particular, it is quite possible that the required efforts to make the subject e-cigarettes as minimally harmful as possible could make them much less harmful and risky than e-cigarettes currently on the U.S. and international markets, thereby dramatically improving the potential public health gains and sharply reducing the size of the related public health risks. It is also likely that the restrictions and requirements outlined here would sharply reduce, if not eliminate, the risk of any new or continued Juul-like expansion of youth e-cigarette use by working effectively to prevent and reduce any future youth initiation, especially among those not already predisposed to becoming smokers or other tobacco product users.

Nevertheless, it is quite possible that FDA's reasonable estimates of the possible future public health impacts from issuing the permissive order would not clearly be AFPPH unless FDA also took additional action to prevent and reduce harm-increasing e-cigarette use without disproportionately decreasing harm-reducing uses. One good possibility (which the White House might allow) would be an FDA rule allowing tobacco products to be sold only at adult-only stores, which would make it much more difficult for youth to obtain either e-cigarettes or smoked tobacco products, which would also reduce youth exposure to any tobacco product advertising, but would keep e-cigarettes equally available to adult smokers as smoked tobacco products.[85] Other options would include a rule requiring all smoked tobacco products to include package inserts informing smokers of the potential harm-reductions from quitting all tobacco product use or, if they could not quit, from switching completely to using legally marketed e-cigarettes or other less-harmful tobacco-nicotine products;[86] targeted public education campaigns to encourage quitting or switching by smokers and to prevent e-cigarette use by youth not highly likely to otherwise become smokers; and more aggressive enforcement of existing restrictions and requirements that apply to smoked tobacco products and their labeling and marketing.[87] To identify additional actions FDA could take to support the ability of PMTA or MRTP permissive orders to be AFPPH or be structured to be AFPPH, FDA could specifically ask for suggestions and related information and analysis from PMTA and MRTP applicants and in related

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[85] *See* Lindblom, *supra* note 39 (providing a more detailed discussion of the public health benefits, and ethical appropriateness, of restricting tobacco product sales to adult-only stores).

[86] Any such product inserts would need to be designed and tested similarly to those inserts previously described for any e-cigarettes receiving permissive PMTA or MRTP orders. *See supra* notes 76–77 and accompanying text.

[87] Such increased enforcement efforts could, for example, require cigarettes falsely labeled as "small cigars" or "little cigars" to comply to those stronger restrictions and requirements that apply to cigarettes compared to cigars. Lindblom et al., *supra* note 75. Or could enforce against packaging, labeling, or phrasing or images in ads for cigarettes and other smoked tobacco products that mislead significant numbers of consumers about their harmfulness either in general or relative to other cigarettes. TCA § 903(a)(1) & (7), 21 U.S.C. § 387c(a)(1) & (7) (2018); *see also* Disc. Tobacco City & Lottery, Inc. v. United States, 674 F.3d 509, 535 (6th Cir. 2011); Lempert & Glantz, *supra* note 72; Meghan Moran et al., *Beyond 'Natural': Cigarette Ad Tactics that Mislead about Relative Risk*, 4 TOBACCO REG. SCI. (2018), https://www.ingentaconnect.com/contentone/trsg/trs/2018/00000004/00000005/art00001 [https://perma.cc/F27D-8USJ].

efforts to secure comments from experts and any other interested parties on pending PMTA or MRTP applications or proposed orders.[88]

After FDA had completed all the above-described procedures to take all available, permitted steps to minimize the likelihood and size of all the possible health harms issuing a permissive PMTA or MRTP order for might cause (without reducing or while increasing the likelihood and size of its probable net public health gains), it is quite likely that FDA's own experts, consulted public health and ethics experts, and other interested parties without a financial self-interest would generally agree that running the risks to secure the probable benefits would not only certainly be defensible in a court of law but also clearly justified as ethically AFPPH.[89] If that were the case, FDA would issue the permissive order, along with strong post-market reporting by the applicant and other post-market surveillance so that remedial steps could quickly be implemented if the marketing of the product began to produce unexpected harms or not secure expected benefits. But if there were any significant doubt or uncertainty, the protective purpose of the PMTA and MRTP provisions and the TCA's overriding purpose of reducing tobacco-related health harms and protecting the public health would mandate an order denying the application.

CONCLUSION

As this example of a possible e-cigarette PMTA or MRTP application shows, there are a remarkably large number of procedural and substantive ways that FDA could readily ensure that any permissive PMTA and MRTP final orders the agency might issue in the future are much more AFPPH, less arbitrary or capricious, and more ethically appropriate than the ones it has issued to date.[90]

To make that happen, FDA first needs to clarify how it will be interpreting the remaining gray areas of the AFPPH standard and how FDA will be applying the standard in the PMTA and MRTP contexts. Simply following common sense and applicable not-arbitrary-or-capricious case law tells us that the AFPPH standard cannot allow PMTA or MRTP orders to create any new health risks or harms unnecessary for securing the orders' larger and more likely net public health gains. Just by acknowledging that, and acting accordingly, FDA would provide much clearer, accurate, and detailed requirements and guidelines for PMTA and MRTP applicants,

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[88] As discussed above, if FDA were able to take enough stronger new actions to prevent and reduce smoking that could also make issuing permissive PMTA or MRTP orders unnecessary for rapidly minimizing smoking and its harms, that would simplify matters by making any new permissive orders not AFPPH. *See supra* notes 39–41 and accompanying text.

[89] Using the phrase "generally agree" means only to recognize that complete unanimity among all internal and external experts and other consulted parties is likely impossible. It would still require a clear general consensus, with only a relatively few conflicting outlier views. The reference to other interested parties "without a financial self-interest" simply recognizes the fact that those with a financial interest (e.g., the applicant or other members of the tobacco industry, broadly defined) would almost certainly provide biased evaluations that would not be relevant. As described above, FDA should also improve the quality of its own expert evaluations, as well as those provided by consulted experts or others, by ensuring that the evaluations are done within the legal constraints of the TCA and other applicable laws (e.g., are not based on ethical or other goals or considerations incompatible with the AFPPH or not-arbitrary-or-capricious standards), carefully consider the various previously listed factors relevant to making such evaluations, and possibly guide some of the evaluations to try to obtain expert and other views from behind a Rawlsian veil of ignorance. *See supra* notes 46–47 and accompanying text.

[90] Lindblom, *supra* note 6.

such as those that have been outlined here. Simply acknowledging this fundamental aspect of the AFPPH standard would also provide much clearer and effective criteria and guidance for FDA's own in-house evaluations of the applications and the possible final orders.

But FDA needs to go further. After taking advantage of all readily available measures to eliminate any unnecessary underlying health harms and risks caused by allowing the subject product's marketing, and otherwise making the possible permissive PMTA or MRTP order as ethically appropriate as possible, FDA needs to explain how it will determine whether the estimated likelihood and size of the potential net public health gains from issuing a permissive order makes running the inevitable associated risks of a possible negative net public health impact AFPPH.

As shown here, there are a number of thoughtful ways FDA could do those evaluations consistently with the protective purpose of the PMTA and MRTP provisions and the public health goals of the TCA. But a key challenge for FDA is that there cannot be any public health or ethical justification for issuing a permissive PMTA or MRTP order that creates new individual or subpopulation health harms and new risks to the public health unless the order will accelerate or increase overall tobacco control progress. That means that FDA cannot find any harmful or risky permissive PMTA or MRTP order AFPPH or otherwise legally viable or ethically appropriate unless FDA is not able to issue new tobacco control rules or take other tobacco control actions that would reduce tobacco-related harms much more quickly and sharply without the kinds of new health harms and risks inherent in allowing the commercial marketing of harmful and addictive PMTA or MRTP tobacco products.

Since receiving its extraordinary, powerful tobacco control authorities in 2009, FDA has not been able to issue any such rules or take any other actions to reduce tobacco-related deaths and harms substantially, much less to minimize them as quickly as possible. The blame has lied largely in the White House, marked by apathy during the Obama Administration and perhaps hostile opposition during the Trump Administration.[91] But FDA and other government officials could be doing much more. Regardless of agency policies and the possibility of retaliation, they could be speaking out about the need for much more aggressive FDA action to reduce the unnecessary death, disease, and economic harms caused by smoking and other tobacco use and they could be focusing media, congressional, and public attention on the reasons FDA has not been able to do what the TCA clearly empowered and intended FDA to do. Playing an insider's game to try to secure tobacco control progress might have made sense at some point. But it has now been more than ten years with no major FDA-prompted tobacco control progress, and a strong case can be made that FDA inaction has even made things worse by enabling the new explosion of youth e-cigarette use.[92]

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[91] *See, e.g.*, Nathaniel Weixel, *Top Trump Official Questions FDA Tobacco Oversight as Vaping Ban Looms*, THE HILL (Nov. 8, 2019), https://thehill.com/policy/healthcare/469618-top-white-house-official-questions-fda-tobacco-role-as-vaping-ban-looms [https://perma.cc/WCH7-3T8S]; *see also* C-SPAN, *User Clip: Joe Grogan—White House Domestic Policy Council—Discusses E-Cigarette Regulation* (Nov. 8, 2019), https://www.c-span.org/video/?c4828413/user-clip-joe-grogan-white-house-domestic-policy-council [https://perma.cc/68PN-Z5R5]; Eric N. Lindblom, *What Tobacco Control Rules Would an Ethically Responsible FDA Implement (If the White House Would Let It)? Would a Nicotine-Reduction Rule Pass Muster?* (in press) (on file with author).

[92] *See, e.g.*, Katie Thomas & Sheila Kaplan, *E-Cigarettes Went Unchecked in 10 Years of Federal Inaction*, N.Y. TIMES (Oct. 14, 2019), https://www.nytimes.com/2019/10/14/health/vaping-e-cigarettes-fda.html [https://perma.cc/W3TR-AD9C].

Meanwhile, roughly five million people have died prematurely from smoking and other tobacco use since FDA first received its extensive tobacco control authorities, with many more to come if FDA does not take more effective and powerful action.[93]

Ethical analysis can be difficult, given competing ethical perspectives and values. As we have seen, for example, it is not easy, and perhaps impossible, to develop any bright-line ethical guidance as to what exact levels of possible health harms and risks should ethically be tolerated to secure more probable public health gains. But there is no ethical ambiguity or excuse for the absence of any strong FDA rules to quickly and sharply reduce tobacco-related harms and costs. Nor is there any ethical excuse or justification for FDA's more internal failure to make its permissive PMTA and MRTP rulings much more AFPPH and otherwise more legally and ethically appropriate, even if political and bureaucratic pressures and obstacles make truly AFPPH determinations impossible.

[93] Bolger, *supra* note 1.