

Non-Therapeutic Uses and the FDA

Patricia J. Zettler

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Patricia J. Zettler^{*}

Abstract

Although debates about the FDA's gatekeeping role for new drugs and devices often—and understandably—focus on its application to important therapies for patients, the FDA's premarket review authorities also extend to non-therapeutic uses of drugs and devices. For example, technologies intended to enhance the cognitive or athletic performance of healthy individuals, breast implants used for solely aesthetic reasons, drugs that eliminate frown lines, and recreational drugs used to produce a “high” or some other biological impact might all fall within the agency's drug and device jurisdiction. This Article explores how the FDA has implemented its premarket review authorities for such non-therapeutic uses of drugs and devices to further understanding of the FDA's gatekeeping function. It argues that, at least for aesthetic uses, the agency has not treated non-therapeutic uses dramatically differently than therapeutic uses. The agency has authorized non-therapeutic uses even when they are associated with small benefits, serious risks, or both, and will accept various forms of effectiveness evidence for non-therapeutic uses including subjects' own evaluations of the effects. This approach to authorizing non-therapeutic uses of drugs and devices, at first blush, may seem inconsistent with the FDA's role as a consumer protection agency charged with protecting and promoting the public health. But this Article demonstrates that numerous different approaches to regulating non-therapeutic uses could be consistent with the consumer protection and information-related purposes of premarket review.

^{*} Patricia J. Zettler is an associate professor at Georgia State University College of Law. For helpful discussion and comments, the author would like to thank Sam Halabi, Erika Lietzan, and the participants in the Research Roundtable on Permits, Licenses, and the Administrative State at the Center for the Study of the Administrative State at George Mason University's Antonin Scalia Law School, the Regulation and Innovation in the Biosciences Workshop at Washington University in St. Louis, the Wiet Life Science Law Scholars Conference at Loyola University Chicago School of Law, and the faculty workshop at University of North Carolina School of Law. This project was supported by the Center for the Study of the Administrative State and a summer research grant from Georgia State University College of Law.

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INTRODUCTION

Each fall as Halloween approaches, stories of the dangers of costume contact lenses—lenses that change the consumer’s eye color or give the appearance of, for example, cat or zombie eyes—saturate the media.¹ News reports tell of consumers who have contracted serious eye infections or suffered injuries, such as corneal tears, leading to years of medical treatment, surgeries, and for some, permanent damage to their vision or blindness.² A common theme in these stories is that the injured consumers believed that the lenses were safe because they believed that the U.S. Food and Drug Administration (FDA) had evaluated the lenses.³

In many ways, this belief makes sense. Notwithstanding the fact that costume lenses have no therapeutic value—they do not correct sight nor address disease in any way—they pose risks similar to those posed by contact lenses that correct the wearers’ vision and that are commonly understood to be medical devices subject to the FDA’s premarket authorization processes.⁴ Indeed, the FDA *does* regulate all contact lenses, regardless of whether they are corrective or decorative, as devices that require premarket authorization from the agency.⁵

¹ See, e.g., *Consult an Eye Care Professional if Your Halloween Costume includes Scary Eyes*, REUTERS (Oct. 5, 2018), <https://www.prnewswire.com/news-releases/consult-an-eye-care-professional-if-your-halloween-costume-includes-scary-eyes-300725224.html>; Kasandra Brabaw, *You’ll Never Use Halloween Contact Lenses After Reading This Teen’s Horrific Story*, Refinery29 (Oct. 16, 2017), <https://www.refinery29.com/2017/10/176827/colored-contacts-halloween-costume-eye-damage>; Tara Edwards, *Local Teen Left Partially Blind After Buying Costume Contacts at Gibraltar Trade Center*, WXYZ Detroit (Oct. 28, 2015), <https://www.wxyz.com/news/region/macomb-county/local-teen-left-partially-blind-after-buying-costume-contacts-at-gibraltar-trade-center>; Venessa Wong, *Those Colored Contact Lenses Can Serious Damage Your Eyes and People Are Worried*, BuzzFeed (Nov. 1, 2017), https://www.buzzfeed.com/venessawong/theres-a-crackdown-on-popular-colored-contact-lenses?utm_term=.ngg3gdJa7#.xcwgYVNdb.

² See, e.g., *id.*

³ See, e.g., *id.*

⁴ See U.S. FOOD & DRUG ADMIN., GUIDANCE: DECORATIVE, NON-CORRECTIVE CONTACT LENSES (Nov. 24, 2006) [hereinafter “DECORATIVE LENSES GUIDANCE”], <https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM071578.pdf>.

⁵ In 2005 Congress amended the Federal Food, Drug, and Cosmetic Act to expressly provide that all contact lenses, regardless of whether they are corrective, are devices within FDA jurisdiction. See, e.g., 21 U.S.C. 360j(n); DECORATIVE LENSES GUIDANCE, *supra* note 4. Many of the news reports of injuries, however, appear to have involved decorative lenses that did not go through the required FDA premarket authorization process and were sold illegally without a prescription. See, e.g., Edwards, *supra* note 1.

Decorative contact lenses, therefore, help to illustrate the vast range of products that can require prior authorization from the FDA before marketing. Although debates about the FDA's premarket authorization of new drugs and devices often—and understandably—focus on the agency's oversight of products that are important therapies for patients,⁶ the FDA's gatekeeping role also extends to *non-therapeutic* uses of drugs and devices. This is generally because the Federal Food, Drug, and Cosmetic Act (FDCA) broadly defines “drugs” and “devices.”⁷ Under the FDCA, drugs and devices are not only products intended to address disease, but also products “intended to affect the structure or any function of the body”⁸ such as technologies intended to enhance the cognitive or athletic performance of healthy individuals, breast implants intended as solely cosmetic improvements, drugs for hair loss, and recreational drugs used to produce a “high” or some other biological impact.⁹

That the FDA's premarket authorization authorities can apply to such non-therapeutic uses of drugs and devices raises the question of how the agency should assess such uses. Scholars are hotly divided over this question, with a particular focus on whether the government should account

⁶ For example, the long-standing debate about terminally and seriously ill patients' pre-approval access to experimental drugs and devices focuses not just on the FDA's role in authorizing therapeutic products, but on that role in the context of therapeutic products intended for very sick patients that lack good treatment options. *See, e.g.,* Lewis A. Grossman, *AIDS Activists, FDA Regulation, and the Amendment of America's Drug Constitution*, 42 AM. J.L. & MED. 687 (2016).

⁷ Certain types of drug products—including vaccines, viruses, proteins, therapeutic serums, and analogous products—also meet the definition of a biological product under the Public Health Service Act. 21 U.S.C. § 262(i). For example, gene therapies generally are both biological products and drugs. Although the precise wording of statutory standard for FDA authorization of biological drug products differs from that for traditional small molecule drugs, the agency generally interprets that standard to be equivalent to the “safe and effective” standard for non-biological drug products, and otherwise regulates biological and traditional small molecule drugs similarly. *Id.* § 262(a). For simplicity, therefore, this Article uses the term “drug” to include both traditional small molecule drugs and biological products, and focuses its discussion on the language in the FDCA. *See, e.g.,* U.S. Food & Drug Admin., FDA 101: Regulating Biological Products, <http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm048341.htm>.

⁸ 21 U.S.C. § 321(g), (h).

⁹ *See, e.g.,* United States v. Travia, 180 F. Supp. 2d 115 (D.D.C. 2001); Patricia J. Zettler, *What Lies Ahead for FDA Regulation of tDCS Products?*, 3 J.L. & BIOSCI. 318 (2016); Patricia J. Zettler et al., *Closing the Regulatory Gap for Synthetic Nicotine Products*, B.C. L. REV. (forthcoming 2018); U.S. Food & Drug Admin., Regulatory History of Breast Implants in the U.S., <https://www.fda.gov/medicaldevices/productsandmedicalprocedures/implantsandprosthetics/breastimplants/ucm064461.htm>; U.S. Food & Drug Admin., Propecia Labeling, https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/020788s024lbl.pdf.

for social and moral concerns about non-therapeutic interventions.¹⁰ But the standards for FDA authorization of drugs and devices require only that the relevant showing of the product's safety and effectiveness be made—and “safety and effectiveness” is generally interpreted to mean that the product's benefits must outweigh its health-related risks, for the uses describing in its labeling.¹¹ That is, regardless of whether the FDA should consider the social and moral implications of non-therapeutic technologies, the agency's enabling statutes currently do not permit it to do so.¹²

Although the FDA cannot consider social and moral concerns in evaluating non-therapeutic uses of drugs and devices, the agency is not necessarily left with an easy task. The standards for drug and device authorization in the FDCA give the agency significant discretion to determine what amount and types of evidence are sufficient to show that a specific use of a drug or device has a favorable benefit-risk ratio.¹³ Even in the context of clearly therapeutic uses that are often agreed to be highly

¹⁰ See, e.g., Dov Fox, *Safety, Efficacy, and Authenticity: The Gap Between Ethics and Law in FDA Decisionmaking*, 2005 MICH. ST. L. REV. 1135 (2005); Francis Fukuyama & Franco Furger, *Beyond Bioethics: A Proposal for Modernizing the Regulation of Human Biotechnologies*, 2 INNOVATIONS: TECHNOLOGY, GOVERNANCE & GLOBALIZATION 117 (2007); Henry T. Greely, *Remarks on Human Biological Enhancement*, 56 U. KAN. L. REV. 1139 (2008); Matt Lamkin, *Regulating Identity: Medical Regulation as Social Control*, 2016 B.Y.U.L. REV. 501 (2016); Gary Marchant et al., *Regulatory Frontiers: Integrating Social and Ethical Concerns Into Regulatory Decision-Making for Emerging Technologies*, 11 MINN. J.L. SCI. & TECH. 345 (2010); Maxwell J. Mehlman, *How Will We Regulate Genetic Enhancement?*, 34 WAKE FOREST L. REV. 671, 702 (1999); cf. Nicholas S. Fitz et al., *Public Attitudes Toward Cognitive Enhancement*, 7 NEUROETHICS 173 (2014) (describing concerns about cognitive enhancement).

¹¹ 21 U.S.C. §§ 355(d), 360c(f)(2), 360e(d), 360(k); 42 U.S.C. § 262(a).

¹² See, e.g., U.S. Food & Drug Admin., FDA's Response to Public Comment on the Animal Cloning Risk Assessment, Risk Management Plan, and Guidance for Industry, <http://www.fda.gov/AnimalVeterinary/SafetyHealth/AnimalCloning/ucm05549> (“the agency has not been charged with addressing moral, religious, or ethical issues associated with animal cloning”); see also Fox, *supra* note 10, at 1195 (arguing that Congress should amend the FDCA to permit the FDA to consider the ethical implications of enhancement technologies); Marchant et al., *supra* note 10 (noting that the FDA lacks the authority to consider social and ethical concerns in its authorization decisions). Of course, the line between what is a health-related concern and what is a social or moral one is not always clear, and at times government regulators, including the FDA, have commingled social, moral, and health-related considerations. See, e.g., Lisa Heinzerling, *The FDA's Plan B Fiasco: Lessons for Administrative Law*, 102 GEO L.J. 927, 928 (2014); see also Patricia J. Zettler et al., *Implementing A Public Health Perspective in FDA Drug Regulation*, 73 FOOD & DRUG L.J. 221, 255 (2018) (making a similar point); Craig Konnoth, *Drug's Other Side Effects* (manuscript on file with author) (arguing that FDA should take a broad approach to the evidence relevant to its approval decision).

¹³ See, e.g., 21 C.F.R. § 314.105(a) (“FDA is required to exercise its scientific judgment to determine the kind and quantity of data and information an applicant is required to provide for a particular drug to meet the statutory standards”).

valuable, the agency's interpretation of these authorization standards can be controversial.¹⁴ As one example, the FDA approves some cancer drugs based on evidence of the drug's effect on a surrogate rather than a clinical endpoint—such as evidence that a drug shrinks a tumor, rather than evidence that it prolongs patients' lives.¹⁵ Some researchers have criticized this approach on the ground that, too often, a drug's effect on a surrogate endpoint is not known to predict meaningful clinical outcomes, and therefore many approved drugs have uncertain benefits for patients.¹⁶ Other commentators, to the contrary, have criticized the FDA's approval processes for such therapies as too onerous, setting the bar for approval too high, or questioned the need for FDA authorization at all.¹⁷

¹⁴ See, e.g., Caroline Chen, *FDA Repays Industry by Rushing Risky Drugs to Market*, PROPUBLICA (June 26, 2018), <https://www.propublica.org/article/fda-repays-industry-by-rushing-risky-drugs-to-market>; cf. Jonathan J. Darrow, *Pharmaceutical Efficacy: The Illusory Legal Standard*, 70 WASH. & LEE L. REV. 2073, 2077 (2013) (arguing that the statutory approval standard for drugs does not “require[] drugs to have anything more than next-to-zero levels of efficacy”); Cynthia M. Ho, *Drugged Out: How Cognitive Bias Hurts Drug Innovation*, 51 SAN DIEGO L. REV. 419 (2014) (examining the ways in which cognitive bias contributes to an environment in which the pharmaceutical industry engages in only “modest innovation”).

¹⁵ See, e.g., Julie A. Beaver et al., *A 25-Year Experience of U.S. Food and Drug Administration Accelerated Approval of Malignant Hematology and Oncology Drugs and Biologics*, 4 J. AM. MED. ASS'N ONCOLOGY 849 (2018).

¹⁶ See, e.g., Robert Kemp & Vinay Prasad, *Surrogate Endpoints in Oncology: When Are They Acceptable for Regulatory and Clinical Decisions, and Are They Currently Overused?*, 15 BMC MED. 134 (2017); Chul Kim & Vinay Prasad, *Strength of Validation for Surrogate Endpoints Used in the US Food and Drug Administration's Approval of Oncology Drugs*, 91 MAYO CLINIC PROC. 713, 723 (2016); Matthew Herper, *The FDA Is Basically Approving Everything. Here's the Data to Prove It*, FORBES (Aug. 20, 2015), <https://www.forbes.com/sites/matthewherper/2015/08/20/the-fda-is-basically-approving-everything-heres-the-data-to-prove-it/#65b42fb45e0a> [https://perma.cc/X9YS-9C8R]; David Gorski, *Donald Trump Versus the FDA: Is the Standard of Evidence for Drug Approval Actually Too Low Rather than Too High?*, SCIENCE-BASED MEDICINE (Feb. 6, 2017), <https://sciencebasedmedicine.org/donald-trump-versus-the-fda-part-2/> [https://perma.cc/WGE3-QWLF]; Nicholas S. Downing et al., *Clinical Trial Evidence Supporting FDA Approval of Novel Therapeutic Agents, 2005-2012*, 311 JAMA 368, 368–69 (2014); Nicholas S. Downing et al., *Postmarket Safety Events Among Novel Therapeutics Approved by the U.S. Food and Drug Administration Between 2001 and 2010*, 317 JAMA 1854, 1854 (2017).

¹⁷ See, e.g., C. Frederick Beckner, III, *The FDA's War on Drugs*, 82 GEO. L.J. 529 (1993); Richard A. Epstein, *Against Permittitis: Why Voluntary Organizations Should Regulate the Use of Cancer Drugs*, 94 MINN. L. REV. 1, 4 (2009) Leah Isakov et al., *Is the FDA Too Conservative or Too Aggressive?: A Bayesian Decision Analysis of Clinical Trial Design 1* (Nat'l Bureau Econ. Research, Working Paper Ser. No. 21499, 2015), https://papers.ssrn.com/sol3/papers.cfm?abstract_id=2641547 [https://perma.cc/E42D-XDPM]; Robert Kocher & Bryan Roberts, *The Calculus of Cures*, 370 NEW ENG. J. MED. 1473, 1474 (2014); Jason Briggeman et al., *The Proper Role of the FDA for the 21st*

When a product is not intended to address disease but is instead intended for a non-therapeutic purpose, the question of how the agency should operationalize benefits and risks—or whether it should have a gatekeeping role at all—may be even more controversial. On the one hand, the value placed on non-therapeutic uses may be so subjective as to compromise the FDA’s ability to meaningfully weigh a product’s benefits and risks for the use, making it difficult for the agency to refuse to authorize a product and, perhaps, to serve its public health mission.¹⁸ On the other hand, because the benefits of non-therapeutic uses of drugs and devices are generally viewed as “less important” than those of therapeutic uses,¹⁹ it may be that the FDA could (or should) authorize only those non-therapeutic products associated with minimal risks, large benefits, or both.²⁰ Such an approach may provide the greatest level of protection for consumers but also may create an effectively insurmountable barrier to gaining permission to market many non-therapeutic uses and significantly narrow consumer choice.

This Article provides an account of how the FDA implements its premarket review authority for non-therapeutic uses to further understanding of how the agency exercises its powerful—and extensive—gatekeeping role for drugs and devices. It demonstrates that a careful review of past FDA actions on non-therapeutic uses of drugs and devices reveals that, when the agency weighs the risks and benefits of non-therapeutic uses, it has not viewed non-therapeutic uses as dramatically less beneficial than therapeutic ones and has been willing to authorize certain

Century, https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3191411; cf. Ralph F. Hall, *Right Question, Wrong Answer: A Response to Professor Epstein and the "Permititis" Challenge*, 94 MINN. L. REV. HEADNOTES 50 (2010).

¹⁸ See, e.g., Mehlman, *supra* note 10, at 701 (“The example of liposuction devices for weight reduction . . . where the benefit is purely cosmetic, illustrates the agency’s difficulties: how can the government conclude that a risk of complications so clearly outweighs the subjective value to patients of an improvement in appearance that a liposuction device, assuming that it actually does remove fatty deposits, should not be approved because it is unsafe or ineffective?”). Relatedly, regardless of the subjective value of a non-therapeutic use, it may be challenging to design studies that ascertain whether a product is effective for that use. For example, with cognitive enhancement technologies, studies may narrowly focus on subjects’ performance on specific tests, while manufacturers and consumers may be interested more broadly in self-improvement. See, e.g., Esther Lanhuis, *Do DIY Brain-Booster Devices Work?*, SCIENTIFIC AMERICAN (Jan. 10, 2017), <https://www.scientificamerican.com/article/do-diy-brain-booster-devices-work/>.

¹⁹ Greely, *supra* note 10, at 1149.

²⁰ Cf. Mehlman, *supra* note 10, at 701 (“A manufacturer can market non-prescription lenses that change eye color under the same conditions as corrective lenses, despite the argument that, given the risks from contact lens use, the ratio of risks to benefits ought to be more favorable to justify the use of lenses for purely cosmetic purposes.”).

non-therapeutic drugs and devices associated with serious risks or minimal benefits (or both).²¹ Returning to the example of decorative contact lenses, they—like corrective lenses—are associated with the risk of corneal ulcers and infections that can lead to blindness, but, nevertheless, have received FDA authorization.²² This is so notwithstanding the fact that the benefits of decorative lenses are transient, purely aesthetic, and undoubtedly to some, trivial.

In other circumstances, the FDA has simply declined to enforce premarket review requirements at all.²³ For some non-therapeutic uses—such as using a non-invasive machine to mechanically exfoliate the face to produce softer, smoother skin—the agency seems to have decided that its gatekeeping role is not needed to serve the agency’s public health mission.²⁴ Indeed, that the agency *can* enforce relevant statutory requirements for premarket review of non-therapeutic drugs and devices, generally does not mean that it *must* enforce those requirements.²⁵

This approach to authorizing non-therapeutic drugs and devices, at first blush, may seem inconsistent with the FDA’s role as a consumer protection agency charged with protecting and promoting the public health.²⁶ But this Article argues that it is not necessarily clear that the agency’s approach runs counter to the roles of FDA gatekeeping. FDA

²¹ See Part III.A., *infra*.

²² See DECORATIVE LENSES GUIDANCE, *supra* note 4.

²³ See Part III.A., *infra*.

²⁴ U.S. FOOD & DRUG ADMIN., GUIDANCE: GENERAL WELLNESS: POLICY FOR LOW RISK DEVICES 7 (July 2016), <https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm429674.pdf>.

²⁵ See, e.g., *Heckler v. Chaney*, 470 U.S. 821, 837 (1985); see also Nathan Cortez, *Regulating Disruptive Innovation*, 29 BERKELEY TECH. L.J. 175, 221 (2014) (“agency discretion may reach its apex versus judicial interference in matters of enforcement”); Catherine Y. Kim, *Presidential Control Across Policymaking Tools*, 43 FLA. ST. U. L. REV. 91, 95 (2015) (describing the “virtual absence of constraints on exercises of enforcement discretion”); Lars Noah, *The Little Agency That Could (Act with Indifference to Constitutional and Statutory Strictures)*, 93 CORNELL L. REV. 901, 902 (2008) (“the FDA enjoys largely unreviewable discretion in deciding whether and how to exercise its enforcement powers”); Jordan Paradise, *Regulatory Silence at the FDA*, 102 MINN. L. REV. 2383, 2388 (2018) (discussing *Heckler v. Chaney*); David Zaring, *Enforcement Discretion at the SEC*, 94 TEX. L. REV. 1155, 1159 (2016) (“Agencies have always enjoyed unfettered discretion to choose their enforcement targets and their policymaking fora.”); *but see* *Cook v. Food & Drug Admin.*, 733 F.3d 1, 7 (D.C. Cir. 2013) (identifying a circumstance in which “clear statutory” language limited the FDA’s discretion to decline to enforce certain requirements).

²⁶ *Cf.* Mehlman, *supra* note 10, at 701 (“A manufacturer can market non-prescription lenses that change eye color under the same conditions as corrective lenses, despite the argument that, given the risks from contact lens use, the ratio of risks to benefits ought to be more favorable to justify the use of lenses for purely cosmetic purposes.”).

gatekeeping for drugs and devices is typically described as serving at least three major purposes: protecting the public from harmful or ineffective products, solving an information asymmetry between patients and drug and device manufacturers, and incentivizing the production of the information needed to understand the effects of drugs and devices.²⁷ Applying these purposes to non-therapeutic uses demonstrates that numerous different approaches to applying its premarket review authorities to non-therapeutic technologies, including the one it seems to have adopted, could be consistent with the agency's mission.²⁸ For example, the FDA reasonably could view consumers—who voluntarily elect to use non-therapeutic products—as in need of less protection than patients, who may be *de facto* forced to use a drug or device by their disease or condition.²⁹ Such a view may justify a flexible approach to weighing a non-therapeutic product's benefits and risks. Moreover, there may be value in the agency treading lightly in this area—where FDA jurisdiction may seem less intuitive—because agency restraint, even if seemingly antithetical to an agency's mission in the short-term, can help agencies reserve serve their missions

²⁷ See, e.g., U.S. FOOD & DRUG ADMIN., MEMORANDUM: PUBLIC HEALTH INTERESTS AND FIRST AMENDMENT CONSIDERATIONS RELATED TO MANUFACTURER COMMUNICATIONS REGARDING UNAPPROVED USES OF APPROVED OR CLEARED MEDICAL PRODUCTS (Jan. 2017) [hereinafter FDA MEMO], <https://www.regulations.gov/document?D=FDA-2016-N-1149-0040>; DANIEL CARPENTER, REPUTATION AND POWER: ORGANIZATIONAL IMAGE AND PHARMACEUTICAL REGULATION AT THE FDA (2010); Daniel Carpenter et al, *Approval Regulation and Endogenous Consumer Confidence: Theory and Analogies to Licensing, Safety, and Financial Regulation*, 4 REG. & GOVERNANCE 383 (2010); Rebecca Dresser & Joel Frader, *Off-Label Prescribing: A Call for Heightened Professional and Government Oversight*, 37 J.L. MED. & ETHICS 476, 483 (2009); Rebecca S. Eisenberg, *The Role of the FDA in Innovation Policy*, 13 MICH. TELECOMM. TECH. L. REV. 345, 347 (2007); Rebecca S. Eisenberg, *The Problem of New Uses*, 5 YALE J. HEALTH POL'Y L. & ETHICS 717, 719–20 (2005); Amy Kapczynski, *Dangerous Times: The FDA's Role in Information Production, Past and Future*, 102 Minn. L. Rev. 2357 (2018); Christopher Robertson & Victor Laurion, *Tip of the Iceberg II: How the Intended-Uses Principle Produces Medical Knowledge and Protects Liberty*, 11 NYU J.L. & LIBERTY 770, 774 (2017); cf. Yaniv Heled, *Regulatory Competitive Shelters*, 76 OHIO ST. L.J. 299, 301 (2015) (describing the FDA's role in supporting innovation); Erika Lietzan, *The Myths of Data Exclusivity*, 20 LEWIS & CLARK L. REV. 91, 150 (2016) (“[S]ome provisions that are viewed as more traditional health-and-safety measures also implement, whether intentionally or incidentally, innovation policy.”); W. Nicholson Price II, *Big Data, Patents, and the Future of Medicine*, 37 CARDOZO L. REV. 1401, 1416 n.71 (2016) (discussing the “intertwined” goals of ensuring the quality, and incentivizing the innovation, of medical algorithms).

²⁸ See Part III.B., *infra*.

²⁹ Cf. Scott Gottlieb, Capturing the Benefits of Competition for Patients, America's Health Insurance Plans' National Health Policy Conference (Mar. 7, 2018), <https://www.fda.gov/NewsEvents/Speeches/ucm599833.htm> (“[i]s a patient really in a position to make an economically-based decision . . . Of course not”).

over the long term.³⁰

For the sake of clarity, a few caveats may be necessary. First, although the FDA regulates drugs and devices throughout their lifecycles—from early development through clinical use after authorization—this Article focuses on the FDA’s premarket authorization decisions. The decision to authorize (or not) the marketing of a drug or device is the FDA’s most blunt regulatory tool. Second, the standards and processes for authorizing the marketing of drugs and devices can be quite different. For example, many device manufacturers obtain permission to market their product by demonstrating that it is substantially equivalent to an existing device, rather than conducting clinical trials to independently demonstrate the new device’s safety and effectiveness—as drug manufacturers often do.³¹ Despite the different processes for obtaining FDA permission to market drugs and devices, however, the underlying purpose of the FDA’s gatekeeping role is the same: as traditionally articulated, to ensure that new drugs and devices are safe and effective for their intended purposes.³² This Article focuses on that overarching purpose of the role of the FDA’s premarket authorization authorities, rather than the details of the varied processes for new drugs and devices.

To develop the Article’s arguments, Part I first describes what is meant by the term “non-therapeutic use.” It then analyzes which non-therapeutic uses are, or are not, subject to the FDA’s drug and device authorities. Part II examines the FDA’s history of assessing the risks and benefits of non-therapeutic uses of drugs and devices, to provide insight into the agency’s approach to regulating such uses. Part III explores the lessons to be learned from this regulatory history of non-therapeutic uses of drugs and devices. It argues that at least three consistent themes emerge from this regulatory history. It then considers these themes in light of the purposes of premarket review, arguing that the FDA’s chosen policy for non-therapeutic uses can be viewed as consistent with the roles that FDA

³⁰ Sharon B. Jacobs, *The Administrative State’s Passive Virtues*, 66 ADMIN. L. REV. 565, 568 (2014).

³¹ 21 U.S.C. § 360(k); *see also* GAO, MEDICAL DEVICES: FDA SHOULD TAKE STEPS TO ENSURE THAT HIGH-RISK DEVICE TYPES ARE APPROVED THROUGH THE MOST STRINGENT PREMARKET REVIEW PROCESS (GAO-09-190) (2009) (reporting that 67% of devices that entered the market from 2003 to 2007 went through this process); Ralph F. Hall & Michelle Mercer, *Rethinking Lohr: Does “SE” Mean Safe and Effective, Substantially Equivalent, or Both?*, 13 MINN. J.L. SCI. & TECH. 737, 739 (2012) (describing this device authorization process).

³² *See, e.g.*, Patricia J. Zettler & Erika Lietzan, *Regulating Medicines in the United States*, in OXFORD HANDBOOK ON COMPARATIVE HEALTH LAW (Oxford University Press, David Orentlicher & Tamara Hervey, eds., forthcoming) (manuscript on file with author); *see also* Eisenberg, *The Role of the FDA in Innovation Policy*, *supra* note 27 (describing the FDA’s role in producing information about drugs).

gatekeeping plays.

I. THE FDA’S JURISDICTION OVER NON-THERAPEUTIC USES

Although stakeholders often focus on the FDA’s role in authorizing the marketing of drugs and devices that serve as therapies for patients, the agency generally has jurisdiction over any product that meets the statutory definition of a drug or device, regardless of whether the product has therapeutic purposes.³³ Moreover, the FDA does not formally distinguish between therapeutic and non-therapeutic uses of products that meet the definition of a drug or device—a drug is a drug, and a device is a device, whether its purpose is therapeutic or not. This Part, thus, describes what this Article means by the term “non-therapeutic use” of a drug or device, in the absence of an FDA definition of the term. It then explains how the FDCA defines “drug” and “device”—analyzing what kinds of non-therapeutic uses fall within the FDA’s drug and device authorities.

A. *Defining Non-Therapeutic Uses*

Although, as discussed further in the following Parts, some of the limits on the FDA’s drug or device jurisdiction implicate the line between therapeutic and non-therapeutic uses of products,³⁴ the FDA has not formally explained—such as through guidance or a regulation—the agency’s thinking about what constitutes a therapeutic or a non-therapeutic use of a drug or device.³⁵ What then, does this Article mean by “non-

³³ To be within the FDA’s jurisdiction, a drug or device (or one of its components) must move in interstate commerce. 21 U.S.C. §§ 321(g)(1), 321(h), 331. Because modern supply chains and production processes generally involve at least one component of a product crossing state or national boundaries, however, this limitation on the FDA’s jurisdiction is rarely relevant. *Cf.* *United States v. Regenerative Scis., LLC*, 741 F.3d 1314 (D.C. Cir. 2014) (finding the required intersection with interstate commerce for an autologous stem cell intervention).

³⁴ *See* Part I.C., *infra*.

³⁵ The agency does have a regulation explaining what constitutes a claim that product affects the structure or function of the body versus a claim that a product addresses disease. 21 C.F.R. § 101.93. But the line between a product use that is intended to affect the structure or function of the body and one that is intended to address disease is not necessarily the same as the line between a therapeutic and non-therapeutic use of that product. This is because some structure/function uses may be therapeutic. For example, “maintains healthy lung function” is a claim that a product is intended to affect the structure or function of the body, but such a claim also seems to have health-related implications—even if related to maintaining health rather than treating a disorder. Regulations on Statements Made for Dietary Supplements Concerning the Effect of the Product on the Structure or Function of the Body, 65 Fed. Reg. 1000, 1018 (Jan. 6, 2000). Additionally, as discussed in more detail in Part I.C. *infra*, in some instances the FDA has

therapeutic uses” of drugs and devices, if not an FDA definition?

This Article uses the term “non-therapeutic use” to describe uses of drugs and devices not intended to maintain health or prevent, treat, or diagnose dysfunction, but instead intended for aesthetic purposes, enhancement, or recreational uses. This terminology is consistent with the literature distinguishing therapeutic and aesthetic, enhancing, and recreational uses of drugs and devices.³⁶ Aesthetic uses refers to those uses intended to alter a person’s appearance in some way, for example infusing human skin cells with a fluorescent protein from jellyfish to make skin glow.³⁷ Enhancement typically refers to those uses that are intended to improve health people’s physical or mental performance to a level beyond their typical states or beyond the statistically normal range for humans.³⁸ For example, students who use stimulants in an effort to improve their academic performance are often described as using drugs for cognitive enhancement.³⁹ Recreational uses refer to those uses of drugs and devices that are “for fun”—or perhaps more simply, for are not therapeutic,

declined to construe device-like products that lack a medical purpose as devices—such as certain exercise equipment. *See* 21 C.F.R. § 890.5350; (2017); *see also* Physical Medicine Devices; General Provisions and Classification of 82 Devices, 48 Fed. Reg. 53032, 5303553,032, 53,035 (Nov. 23, 1983) (“FDA has changed the regulations classifying many physical medicine devices to clarify that the regulations apply only to those products intended for medical purposes”). But in those instances, the FDA has not offered a formal definition of what constitutes a medical purpose, nor has it applied that policy of requiring a medical purpose to all of its jurisdictional determinations regarding whether products are drugs or devices. Finally the FDA’s website offers a succinct definition of “cosmetic devices” as those devices that “are used to improve appearance and do not impart any health benefits.” U.S. Food & Drug Admin., Cosmetic Devices, <https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/CosmeticDevices/default.htm>. This, however, is not a complete definition that encompasses any non-therapeutic uses of drugs nor the full range of non-therapeutic uses for devices.

³⁶ *See, e.g.*, Henry T. Greely et al., *Towards Responsible Use of Cognitive-Enhancing Drugs*, 456 *Nature* 702 (2008); Mehlman, *supra* note 10.

³⁷ *Cf.* Kristen V. Brown, *Genetically Engineering Yourself Sounds Like a Horrible Idea—But this Guy Is Doing it Anyway*, GIZMODO (Nov. 29, 2017), <https://gizmodo.com/genetically-engineering-yourself-sounds-like-a-horrible-1820189351> (describing a biohacker’s attempt to make his skin glow).

³⁸ *See, e.g.*, PRESIDENTIAL COMMISSION FOR THE STUDY OF BIOETHICAL ISSUES, GRAY MATTERS (Vol. 2) at 28 (Mar. 2015), https://bioethicsarchive.georgetown.edu/pcsbi/sites/default/files/GrayMatter_V2_508.pdf; *see also* Greely, *supra* note 10 at 1140 (“[enhancement] is using things not only to repair or bring up the human norm, but also to surpass either the preexisting position or to go to the extreme—to move outside the normal human range”); Fox, *supra* note 10 at 1137–38 (“Enhancements are distinct from other biomedical products in that they are put to uses which extend beyond the goal of preventing disease, repairing disability, and restoring physiological wholeness.”)

³⁹ *See, e.g.*, Greely et al., *supra* note 36.

aesthetic, or enhancing purposes. An individual who inhales nitrous oxide to obtain a high, for instance, is generally described as using a recreational drug.⁴⁰

Of course, where to draw the line between an aesthetic, enhancing, recreational, or a health-related therapeutic use is not always, and perhaps is only rarely, clear.⁴¹ In addition to line drawing questions, commentators have long criticized industry—and pharmaceutical companies, in particular—for “inventing” diseases and proactively muddying the distinction between therapeutic and non-therapeutic uses to sell their products.⁴² For example, disease awareness (or, as the FDA calls it, help-seeking) advertising aims to increase consumers’ awareness that particular symptoms might constitute a treatable condition, such as “overactive bladder,” and typically instruct consumers to “talk to their doctors” about their symptoms. In this way, critics argue, such advertising can medicalize the discomforts of ordinary life in order to increase prescriptions and sell more pharmaceuticals.⁴³

Questions about what counts as therapeutic and non-therapeutic uses—and how the distinction between the two might be manipulated—are important. But this Article does not attempt to resolve them. Instead, it aims to consider how the FDA regulates, and should regulate, non-therapeutic uses of drugs and devices, however “non-therapeutic” is properly defined.

⁴⁰ See, e.g., Aaron Rowe, *Chem Law: The Downside of Getting High on Nitrous Oxide*, WIRED (Dec. 9, 2017), <https://www.wired.com/2007/12/chem-lab-the-do/>.

⁴¹ See, e.g., Henry T. Greely, *Direct Brain Interventions to Treat Disfavored Human Behaviours: Ethical and Social Issues*, 91 CLINICAL PHARMACOLOGY & THERAPEUTICS 163 (2012) (“Behaviors do not come naturally labeled as ‘disease’ and ‘nondisease;’ humans make those distinctions, and, as various versions of the Diagnostic and Statistical Manual of Mental Disorders reveal, we regularly change them.”); Matt Lamkin, *Legitimate Medicine in the Age of Consumerism* (manuscript on file with author) (critiquing the divide between legitimate medicine and drug misuse in the federal Controlled Substances Act). For example, imagine a person with occasional mild social anxiety who sometimes uses a benzodiazepine, such as Xanax—a drug that the FDA-approved labeling describes as not appropriate for “[a]nxiety or tension associated with the stress of everyday life”—because it makes her “feel good.” Does this behavior constitute treatment of her mild social anxiety? Is the behavior enhancement because a benzodiazepine is too strong of a treatment for her low-level anxiety? Is this behavior recreational drug use, because the benzodiazepine makes her feel good, perhaps akin to some illicit drugs? Does it matter if a physician prescribed her the drug, or if instead she obtained it without a prescription, for example, by using pills prescribed to her friend? See, e.g., Lamkin, *Legitimate Medicine*, *supra*, (asking similar questions).

⁴² See, e.g., Ray Moynihan et al, *Selling Sickness the pharmaceutical industry and disease mongering*, 324 BR. MED. J. 886 (2002).

⁴³ See, e.g., *id.* Research has shown direct-to-consumer advertising does prompt patients to ask their physicians for medications, and that, in turn, does increase prescribing rates.

For that reason, this Article focuses on examples of uses of drugs and devices that commentators generally agree are non-therapeutic, such as the use of Botox to reduce the appearance of facial wrinkles or the use of decorative contact lenses to change the appearance of the users' eyes.⁴⁴ Such uses of drugs and devices, also, notably are not generally covered by health insurance plans, which typically reimburse for "medically necessary" services.⁴⁵

Additionally, this Article uses the term non-therapeutic *uses*, rather than non-therapeutic *products*, because the FDA's regulatory scheme generally focuses on particular uses of a products. Regardless of a drug or device's route through the FDA's premarket review processes, the FDA's authorization decision is specific to the product's intended use.⁴⁶ That is, the FDA does not assess a product's benefits and risks as a general matter. Rather it assesses the benefits and risks for the specific use described in the product's proposed labeling. Accordingly, the FDA might judge the exact same product as safe and effective for one use but not for another. For example, at one point the FDA had approved the drug Avastin (bevacizumab) for use in breast, colon, lung, kidney, and brain cancers—but in 2011 it withdrew its approval of Avastin for use in metastatic breast cancer after determining the drug had not been demonstrated safe and effective for that one use.⁴⁷ The drug, however, remains approved for the other uses, for which, in the FDA's view, there continues to be evidence that the drug's benefits outweigh its risks.⁴⁸

B. The Broad Scope of the Drug and Device Definitions

Under the FDCA, a wide range of products are "drugs" and "devices." Drugs and devices are defined as products that are "*intended for* use in the diagnosis, cure, mitigation, treatment, or prevention of disease" or "*intended to affect the structure or any function of the body*" (emphasis added).⁴⁹ Key for determining whether a technology is a drug or a device

⁴⁴ See, e.g., Fox, *supra* note 10; Greely, *supra* note 10; Lamkin, *supra* note 10.

⁴⁵ "Medically necessary" is broad enough to include uses of drugs and devices that are health-related, but not disease-focused—such as pregnancy tests performed in a physician's office or laboratory. But not so broad as to typically include aesthetic, enhancing, or recreational uses of drugs and devices.

⁴⁶ 21 U.S.C. §§ 355(d), 360c(f)(2), 360e(d), 360(k); 42 U.S.C. § 262(a); see also FDA MEMO, *supra* note 27 (describing the reasons for evaluating a product for a particular use).

⁴⁷ See U.S. Food & Drug Admin., Avastin Information, <https://www.fda.gov/Drugs/DrugSafety/ucm193900.htm>.

⁴⁸ See Avastin Labeling, https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/125085s323lbl.pdf.

⁴⁹ 21 U.S.C. § 321(g)(1), (h). Devices are distinguished from drugs largely by the

under federal law, therefore, is the product’s “intended use.”⁵⁰ Intended use refers to the “objective intent of the persons legally responsible for the labeling,” which is usually a product’s manufacturer or seller.⁵¹

Typically the requisite intended use is demonstrated by a manufacturer or seller’s public statements suggesting, explicitly or implicitly, that a product is intended to address disease (“disease claims”) or is intended to affect the structure or function of the body (“structure/function claims”).⁵² For example, a manufacturer might state in the labeling for its intravenous drug that the product is “indicated for the treatment of metastatic colorectal cancer,” which would be a disease claim.⁵³ As another example, a manufacturer might market a brain stimulation device for increased athletic “stamina and endurance,” which would be a structure/function claim.⁵⁴ Indeed, because drugs and devices

kinds of items that they are—articles that do not “achieve [their] primary intended purpose through chemical action within or on the body . . . and . . . [are] not dependent on being metabolized” to achieve that purpose. Additionally, devices, unlike drugs, include articles intended for use in the diagnosis of “conditions.” *Id.* at § 321(h). This aspect of the device definition is meant to capture diagnostic tools that are not focused on diseases, but are nevertheless important, such as pregnancy tests.

⁵⁰ 21 C.F.R. § 201.128; 21 C.F.R. § 801.4. The major exception to this principle is contact lenses. In 2003 the FDA stated its view that decorative contact lenses were cosmetics, not devices, “[p]rovided they are not marketed with claims that they effect physical or physiological change.” GUIDANCE FOR FDA STAFF ON SAMPLING OR DETENTION WITHOUT PHYSICAL EXAMINATION OF DECORATIVE CONTACT LENSES (Import Alert #86-10), 68 Fed. Reg. 16520, 16521 (Apr. 4, 2003). Perhaps because non-corrective contact lenses pose the same serious risks as corrective ones do, however, two years later Congress amended the FDCA to expressly state that all contract lenses are devices, eliminating the FDA’s discretion to decide otherwise—and, for this class of products, the need for FDA to establish that the products are intended to affect the structure or function of the body. 21 U.S.C. § 360j(n); DECORATIVE LENSES GUIDANCE, *supra* note 4; *see also* Eric Chan, *The Food and Drug Administration and the Future of the Brain-Computer Interface: Adapting FDA Device Law to the Challenges of Human-Machine Enhancement*, 25 J. MARSHALL J. COMPUTER & INFO. L. 117, 148 (2007) (discussing the FDA’s approach to decorative lenses).

⁵¹ 21 C.F.R. § 201.128; 21 C.F.R. § 801.4. In 2017, the FDA made controversial revisions to its definition of intended use. As of the time of writing, the agency has delayed the effective date indefinitely for the controversial changes. However, the agency did not change the part of the definition discussed here. 82 Fed. Reg. 2193, 2198, 2200 (Jan. 9, 2017); 82 Fed. Reg. 14319, 14320 (Mar. 20, 2017).

⁵² *See, e.g.,* Zettler et al., *Synthetic Nicotine*, *supra* note 9.

⁵³ *Cf.* Avastin Labeling, https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/125085s323lbl.pdf (labeling for a drug indicated for various disease including metastatic colorectal cancer).

⁵⁴ *See, e.g.,* Warning Letter from Steven E. Porter, FDA to Flex Fitness Products and Big Dan’s Fitness (May 25, 2017), <https://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2017/ucm562233.htm>; Zettler, *tDCS*, *supra* note 9.

include many such products intended for use in affecting the structure or function of the body, the scope of the FDA's drug and device jurisdiction is quite broad, covering products commonly understood to be drugs and devices as well as those that are not.

Moreover, although the FDA typically relies on a manufacturer or seller's public claims to determine a product's intended use, such claims are not the only source of evidence for ascertaining intended use.⁵⁵ The FDA's regulations provide that the agency also may consider the "circumstances surrounding distribution,"⁵⁶ and courts have opined that the agency may consider "any relevant source" of evidence of intended use.⁵⁷ A product's design, internal company statements, statements that a company previously made (but no longer makes), and the overall environment in which a product is distributed are all among the other kinds of evidence on which the FDA has relied.⁵⁸ For example, the FDA has taken the position that a

⁵⁵ 21 C.F.R. § 201.128; 21 C.F.R. § 801.4.

⁵⁶ *Id.*

⁵⁷ See, e.g., *Nat'l Nutritional Foods Ass'n v. Mathews*, 557 F.2d 325, 334 (2d Cir. 1977) (The FDA is not bound by the manufacturer's subjective claims of intent . . . Such intent also may be derived or inferred from labeling, promotional material, advertising, and 'any other relevant source.'") (internal citations omitted); 82 Fed. Reg. 2193, 2199 (Jan. 9, 2017) ("the Agency may look to any relevant source to determine intended use"); cf. *Food & Drug Admin. v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120 (2000) (rejecting the FDA attempt to regulate tobacco products as drugs and devices, without disagreeing with the argument that the tobacco products' design was evidence of their intended use).

⁵⁸ See, e.g., *United States v. Storage Spaces Designated Nos. 8 and 49*, 777 F.2d 1363, 1366 n.5 (9th Cir. 1985) (concluding that the "overall circumstances" showed that products labeled as incense were drugs); *Allergan, Inc. v. Athena Cosmetics, Inc.*, 738 F.3d 1350, 1357 (Fed. Cir. 2013) (concluding conclude that a company's *past* claims that its product affected the structure of eyelashes were relevant to an intended use analysis because the company did not materially alter its product's formulation or disavow its previous claims); *Latex Surgeons' Gloves*, 799 F. Supp. at 1285 ("[W]hen a manufacturer has created a market for a product to be used as a device, he or she cannot avoid the reaches of the [FDCA] by stating that the product has a different—and non-regulated use. The Courts have recognized the 'carry-over effect' that is created by a manufacturer's original representations about the product."); *Drug Labeled as "Exachol,"* 716 F. Supp. at 791 (noting that "Courts have recognized that where years later customers purchase a product in reliance on the therapeutic claims of the previous literature marketed with that product, the court may use such literature to determine the intent in marketing the product despite a later disclaimer"); *United States v. Travia*, 180 F. Supp. 2d 115, 119 (D.D.C. 2001) (concluding that unlabeled nitrous oxide sold outside a rock concert was a drug because the "environment provided the necessary information between buyer and seller"); *United States v. Vascular Solutions, Inc.*, 181 F. Supp. 3d 342, 347 (W.D. Tex. 2016) (permitting the use of non-public statements as evidence of intended use); *Nicotine in Cigarettes and Smokeless Tobacco Is a Drug and These Products Are Nicotine Delivery Devices Under the Federal Food, Drug, and Cosmetic Act: Jurisdictional Determination*, 61 Fed. Reg. 44,619, 44,630 (Aug. 28, 1996), available at <https://www.gpo.gov/fdsys/pkg/FR-1996-08-28/pdf/X96-20828.pdf> (relying on product design as evidence of intended use); *Warning*

machine designed to use electrical current to contract facial muscles, in order to tighten skin and reduce wrinkles, is a device “even if no claims were made for its specific use.”⁵⁹ That the agency can establish a product’s intended use based on a wide range of sources further underscores the expansiveness of the FDA’s drug and device jurisdiction.⁶⁰

C. Limits on Premarket Review of Non-Therapeutic Uses

Although the FDA’s drug and device jurisdiction is far-reaching, it is not without limits. Congress, the courts, and the FDA itself have placed limits on the drug and device definitions, and the FDA’s regulatory focus on a specific, intended use of a product places certain non-therapeutic uses outside of the FDA’s premarket review processes. This means that many common non-therapeutic uses of technologies—such healthy individuals using creams intended to reduce the appearance of wrinkles or attention deficit hyperactivity (ADHD) medications to improve cognitive performance—fall outside of the FDA’s drug and device premarket review authorities. Yet, as the discussion below makes clear, these limits do not remove *all* non-therapeutic uses from the agency’s drug and device authorities.

1. The Boundaries of the Drug and Device Definitions

The plain language of the drug and device definitions, arguably, could extend to include commonplace consumer products that very few, if any, would think appropriate for FDA regulation, such as wool sweaters marketed to keep consumers warm in the winter.⁶¹ Perhaps partly for this reason, Congress and the courts, as well as the FDA itself, have placed

Letter from Larry D. Spears, FDA to Salton, Inc. (July 12, 2000) <http://www.casewatch.org/fdawarning/prod/2000/salton.shtml> (relying on product design as evidence of intended use) [hereinafter “Rejuvenique Warning Letter”].

⁵⁹ Rejuvenique Warning Letter, *supra* note 58.

⁶⁰ There is currently debate about the extent to which the FDA can rely on evidence other than a manufacturer or seller’s public claims to show a product’s intended use. 83 Fed. Reg. 11639 (Mar. 16, 2018) (explaining that the FDA is indefinitely delaying the effective date of changes to its intended use regulations that retained language explaining that it may rely on company knowledge about consumer intent). Regardless of how this current debate is resolved, however, there are likely to continue to be circumstances in which the FDA may rely on evidence other than a company’s public statements to demonstrate that a product is intended for use in addressing disease or affecting the structure or function of the body. *See, e.g.,* Zettler et al., *Synthetic Nicotine*, *supra* note 9.

⁶¹ *Cf.* Food & Drug Admin. v. Brown & Williamson Tobacco Corp., 529 U.S. 120, 168 (U.S. 2000) (Breyer, J., dissenting) (noting that, taken literally, the definition of a device could include “thermal pajamas”).

certain kinds of non-therapeutic products—that otherwise might satisfy the drug or device definition—outside the scope of the FDA’s drug and device jurisdiction.⁶²

The FDCA expressly defines certain kinds of products, including cosmetics, tobacco products, and dietary supplements, separately from drugs and devices.⁶³ Cosmetics cannot be intended to address disease or affect the structure or function of the body, and instead are intended “for cleansing, beautifying, promoting attractiveness, or altering [] appearance.”⁶⁴ Tobacco products—products “made or derived from tobacco” including e-cigarettes that use tobacco-derived e-liquid—cannot

⁶² Jurisdictional debates also arise over whether a particular intervention—for example, a stem cell procedure—involves a product regulated by the FDA or is, instead, a medical service typically thought of as regulated by the states. *See, e.g.,* *United States v. Regenerative Scis., LLC*, 741 F.3d 1314 (D.C. Cir. 2014). As I have argued elsewhere, however, the product-medical practice distinction is blurry and may not be useful for determining the scope of the FDA’s jurisdiction. Patricia J. Zettler, *Pharmaceutical Federalism*, 92 IND. L.J. 845, 892 (2017); *see also* June Carbone & Jody Lyneé Madeira, *Buyers in the Baby Market: Toward A Transparent Consumerism*, 91 WASH. L. REV. 71, 97–98 (2016) (“FDA, which comprehensively regulates drugs, has typically taken a different approach to medical procedures and human tissue, and thus has had relatively limited involvement in IVF”); Lars Noah, *Ambivalent Commitments to Federalism in Controlling the Practice of Medicine*, 53 U. KAN. L. REV. 149, 173 (2004) (“Given its power to prevent the sale of drugs and medical devices until persuaded of their safety and effectiveness, the FDA undoubtedly affects the practice of medicine, even if only indirectly”); Margaret Foster Riley, *An Unfulfilled Promise: Changes Needed to the Drug Approval Process to Make Personalized Medicine A Reality*, 70 FOOD & DRUG L.J. 289, 308 (2015) (“In 2007, FDAAA introduced potentially far-reaching limits on the practice of medicine doctrine allowing FDA to impose restrictions (e.g. place and mode of use) on approved drugs”); Myrisha S. Lewis, *How Subterranean Regulation Hinders Innovation in Assisted Reproductive Technology*, 39 CARDOZO L. REV. 1239, 1265 (2018) (“In light of the blurring distinctions between medical devices, human tissues, drugs, and the practice of medicine, if the FDA does have jurisdiction over advanced assisted reproductive technologies, it should clearly explain the source of that jurisdiction . . .”).

⁶³ 21 U.S.C. § 321(i), (ff), (rr). A product can meet the definition of both a cosmetic and a drug or device, if it is both intended to both alter appearance and affect the structure or function of the body. In such instances of products that are a combination of a cosmetic and a drug or device, the product is regulated according to the more stringent drug or device rules. *See, e.g.,* U.S. Food & Drug Admin., *Is It a Cosmetic, a Drug, or Both? (Or Is It Soap?)*,

<https://www.fda.gov/cosmetics/guidanceregulation/lawsregulations/ucm074201.htm>.

Unlike cosmetics, a product cannot meet both the definition of a tobacco product or a dietary supplement and of a drug or device, nor may a tobacco product or dietary supplement be combined with a drug or device. *See* 21 U.S.C. § 321(rr)(2), (4); Warning Letter from Deborah M. Autor, FDA to Proctor and Gamble (Oct. 29, 2009), <https://wayback.archive-it.org/7993/20170112063315/http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2009/ucm188361.htm>.

⁶⁴ 21 U.S.C. § 321(i).

be marketed to address disease, but may be marketed as affecting the structure or function of the body as long as the structure/function claims are those that have been customarily made about tobacco (e.g., “satisfying”).⁶⁵ Similarly, dietary supplements—which must contain a dietary ingredient, such as an herb, and not contain approved or studied drug ingredients—may be marketed with structure/function claims but not disease claims.⁶⁶ Through these avenues, many products with non-therapeutic uses, such as a cosmetic cream intended to reduce the appearance of, but not the actual existence of, wrinkles or an herb intended to enhance muscle tone, may reach the market without being subject to the FDA’s drug and device requirements.⁶⁷

Most recently, Congress amended the FDCA, through the 21st Century Cures Act of 2016, to exclude from the device definition software intended “for maintaining or encouraging a healthy lifestyle and is unrelated to the diagnosis, cure, mitigation, prevention, or treatment of a disease or condition.”⁶⁸ Although “encouraging a healthy lifestyle” may suggest that software falling into this non-device category must have a therapeutic, health-related purpose, the FDA has taken the position that this kind of language also encompasses enhancement uses, such as products intended to “enhance learning capacity.”⁶⁹ For example, a video game meant to improve mental acuity—although intended to affect the structure or function of the

⁶⁵ See 21 U.S.C. § 321(rr); *Sottera, Inc. v. FDA*, 627 F.3d 891, 894 (D.C. Cir. 2010); 82 Fed. Reg. 2193, 2208 (Jan. 9, 2017); see also *FDA v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120 (2000) (reaching this conclusion based on the FDA’s statutory authority before the Family Smoking Prevention and Tobacco Control Act of 2009 expressly granted the FDA authority to regulate tobacco products); *Action on Smoking & Health v. Harris*, 655 F.2d 236, 240 (D.C. Cir. 1980) (affirming the FDA’s then-decision to decline to categorize cigarettes as drugs or devices). According to the FDA, a manufacturer’s claim that its tobacco product is “satisfying” is an implicit structure/function claim that amounts to a “euphemism for the delivery of a pharmacologically active dose of nicotine.” 80 Fed. Reg. 57756, 57760 (Sept. 25, 2015).

⁶⁶ 21 U.S.C. § 343(r)(3); 21 C.F.R. §§ 101.14(a)(1), 101.93. In addition, in some circumstances, claims can be made that dietary supplements are intended to reduce the risk of disease (e.g., calcium may reduce the risk of developing osteoarthritis) without triggering the FDA’s drug authorities. See, e.g., U.S. Food & Drug Admin., Label Claims for Conventional Foods and Dietary Supplements, <https://www.fda.gov/food/labelingnutrition/ucm111447.htm>. These kinds of supplements, however, are not particularly relevant to a discussion of non-therapeutic products.

⁶⁷ See, e.g., 65 Fed. Reg. 1000 (Jan. 6, 2000).

⁶⁸ Pub. L. No. 114-255 § 3060, 130 Stat. 1033, 1130 (2016).

⁶⁹ U.S. FOOD & DRUG ADMIN., GUIDANCE: GENERAL WELLNESS: POLICY FOR LOW RISK DEVICES 3 (July 2016), <https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm429674.pdf>.

brain—is likely no longer a device under the FDA’s jurisdiction.⁷⁰

Courts and the FDA itself, also, have opined in some instances that other products that are intended to affect the structure or function of the body fall outside the drug and device definitions. In two cases in the 1960s and 1970s two circuit courts and one district court judge concluded that structure/function claims must be “medical,” “drug-type,” or “therapeutic” in nature to make a product—in those cases, a wrinkle cream—a drug or device.⁷¹ Relying on these cases, the FDA also has stated in a few instances that a product must have a “medical application” to fall within the device definition, specifically.⁷² For example, the agency declined to categorize as devices exercise equipment intended for recreational or athletic purposes and implantable chips to be used for non-medical identification purposes, despite the fact such products are clearly intended to affect the structure or function of the body.⁷³

Although requiring that drugs and devices have a “medical” application on its face might seem to exclude non-therapeutic uses from the FDA’s drug and device authorities, courts have not consistently interpreted the drug and device definitions so narrowly. The courts that suggested that

⁷⁰ *Cf. id.* (describing claims about improving mental acuity as “general wellness claims” “that do not make any reference to disease or conditions”). Before the 21st Century Cures Act was enacted, however, it was the FDA’s policy not to enforce device requirements for many such products, meaning the law may not have changed much in practice. *See id.*; *See* U.S. FOOD & DRUG ADMIN., GUIDANCE: MOBILE MEDICAL APPLICATIONS (Feb. 9, 2015), <https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM263366.pdf>.

⁷¹ *See, e.g.,* *United States v. Article . . . Consisting of 216 Cartoned Bottles, More or Less, Sudden Change*, 409 F.2d 734 (2d Cir. 1969); *United States v. An Article of Drug. . . Line Away*, 415 F.2d 369 (3d Cir. 1969); *United States v. An Article of Drug... Helene Curtis Magic Secret*, 331 F. Supp. 912 (D.Md. 1971) (relying on *Line Away* and *Sudden Change* to conclude that a wrinkle cream was not a drug); *see also* Anna Wexler, *A Pragmatic Analysis of the Regulation of Consumer Transcranial Direct Current Stimulation (tDCS) Devices in the United States*, 2 J.L. BIOSCI. 669, 681 (2015) (discussing these cases).

⁷² PETER HUTT, RICHARD MERRILL, & LEWIS GROSSMAN, *FOOD AND DRUG LAW: CASES AND MATERIALS* 125-28 (2013) (reprinting Letter from Daniel E. Troy, FDA Chief Counsel to Jeffrey N. Gibbs (Oct. 17, 2002)); *see also* *United States v. Undetermined No. of Unlabeled Cases*, 21 F.3d 1026, 1030 (10th Cir. 1994) (Cook, J., dissenting) (“The government concedes that it does not claim that a device which has no medical application could ‘qualify as a device under the FDCA’”); *cf.* William W. Buzbee, *Recognizing the Regulatory Comments: A Theory of Regulatory Gaps*, 89 IOWA L. REV. 1 (2003); Gary E. Gamerman, *Intended Use and Medical Devices: Distinguishing Nonmedical “Devices” from Medical “Devices” Under 21 U.S.C. 321(h)*, 61 GEO. WASH. L. REV. 806, 807 (1993).

⁷³ *See* Letter from Thomas Scarlett, FDA to James V. Lacy, Consumer Product Safety Commission (May 6, 1983); HUTT ET AL., *supra* note 72 at 125-28 (reprinting Letter from Daniel E. Troy, FDA Chief Counsel to Jeffrey N. Gibbs (Oct. 17, 2002)).

structure/function claims must have a “medical” connotation also construed a wide variety of claims, including claims such as “tighten[s] the skin,” to meet that standard.⁷⁴ In other cases, courts simply have not declared that structure/function claims must have a medical, drug-type, or therapeutic connotation to make a product a drug or device.⁷⁵ Likewise, the FDA has in some instances construed non-therapeutic uses of products to be devices—such as injectable dermal fillers intended to eliminate wrinkles or enhance lips, “micro-needling” machines intended to improve the skin’s texture, tone, or color, and products intended for spider vein removal.⁷⁶ Indeed, if it were true that products must have medical uses—narrowly construed—to meet the definition of a device, it may not have been necessary for Congress to remove software intended for general wellness uses from the definition of a device, for example.⁷⁷ In short, although questions may remain about precisely where the boundaries of the FDA’s drug and device jurisdiction lie, it is clear that many non-therapeutic uses remain subject to the FDA’s

⁷⁴ *Line Away*, 415 F.2d at 372; *see also Sudden Change*, 409 F.2d at 742; *but see Helene Curtis Magic Secret*, 331 F.Supp. at 915 (concluding that claims a wrinkle cream with claims similar to those described in *Line Away* was not a drug).

⁷⁵ *See, e.g., United States v. Storage Spaces Designated Nos. 8 & 49 Located at 277 E. Douglas, Visalia, Cal.*, 777 F.2d 1363, 1366 (9th Cir. 1985); *Nutrilab, Inc. v. Schweiker*, 713 F.2d 335, 339 (7th Cir. 1983); *United States v. Travia*, 180 F. Supp. 2d 115 (D.D.C. 2001); *see also* Warning Letter from Monica R. Maxwell, FDA to Arco Globus Trading LCC (Dec. 11, 2017), <https://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2017/ucm588493.htm> (concluding that products marketed as producing a “euphoria” are drugs under the FDCA); Warning Letter from Michael Dutcher, Dir., FDA Minneapolis Dist., to ALV SUPPLEMENT DIRECT, <https://www.fda.gov/iceci/enforcementactions/warningletters/2016/ucm489374.htm> Timothy Meyer, *alvSupplement Direct* (Mar. 3, 2016), <https://www.fda.gov/iceci/enforcementactions/warningletters/2016/ucm489374.htm> (concluding that products marketed as “boosting energy,” burning fat, and “increase[ing] focus” are drugs); *cf. United States v. Undetermined No. of Unlabeled Cases*, 21 F.3d 1026, 1028 (10th Cir. 1994) (“The [device] definition does not define the term “diagnosis” nor limit diagnostic devices to those used prior to medical treatment.”).

⁷⁶ *See, e.g., U.S. Food & Drug Admin., Warning Letters Highlight Differences Between Cosmetics and Medical Devices*, <https://www.fda.gov/cosmetics/complianceenforcement/warningletters/ucm081141.htm>.

The FDA’s seemingly contradictory positions be result from the agency broadly construing the term “medical.” For example, in 1993 the agency explained that it considered drugs intended to stop the habit of nailbiting to be intended to prevent disease, because nailbiting can make infection more likely. *See Nailbiting and Thumbsucking Deterrent Drug Products for Over-the-Counter Human Use*, 58 Fed. Reg. 46749 (Sept. 2, 1993). It also may be that the FDA did not accurately describe its overall policy in the documents in which it claimed specific without medical applications were not devices.

⁷⁷ Pub. L. No. 114-255 § 3060, 130 Stat. 1033, 1130 (2016).

drug and device authorities.⁷⁸

2. Off-Label Uses

When a particular product is a drug or device, the FDA, nevertheless, may lack authority to review and authorize a non-therapeutic use of that product if the use is “off-label.”⁷⁹ This is because each of the FDA’s premarket authorization processes evaluate a product for its intended use.⁸⁰ That is, the agency’s weighing of the product’s risks and benefits, and its authorization decision, is not for the product as a whole, but rather for the particular use that the manufacturer has proposed—to address a particular disease or condition, or have a particular effect on the body, for a specific patient population, and, for drugs, at a specified dose and in a specified

⁷⁸ It is worth noting that the FDA may continue to be able to successfully assert jurisdiction over such uses even if formal doctrines of judicial deference to agency positions wane. *Cf.* Cary Coglianese, *Chevron's Interstitial Steps*, 85 GEO. WASH. L. REV. 1339, 1344 (2017) (describing *Chevron* and “the emerging criticism of its deference principle”); Kristin E. Hickman, *The (Perhaps) Unintended Consequences of King v. Burwell*, 2015 PEPP. L. REV. 56, 58 (2015) (arguing that *King v. Burwell* “reflects a careful effort by Chief Justice Roberts to accomplish, through alternative framing, a broader curtailment of *Chevron*'s scope that he advocated unsuccessfully two terms earlier in *City of Arlington v. FCC*”); Christopher J. Walker, *Attacking Auer and Chevron Deference: A Literature Review*, 16 GEO. J.L. & PUB. POL'Y 103 (2018) (describing the arguments in favor of eliminating or narrowing *Chevron* and *Auer* deference). For example, judicial deference to the FDA’s interpretations of the FDCA pre-dates *Chevron*. *See, e.g.*, *Bacto-Unidisk*, 394 U.S. at 791-92; *United States v. Rutherford*, 442 U.S. 544, 553 (1979); *Premo Pharmaceutical Laboratories, Inc. v. United States*, 629 F.2d 795 (2d Cir. 1980); *see also* Zettler et al., *Implementing a Public Health Perspective*, *supra* note 12 at 247 n.166 (making a similar point); *cf.* Kent Barnett & Christopher J. Walker, *Chevron in the Circuit Courts*, 116 MICH. L. REV. 1, 53 (2017) (reporting a study finding that the FDA was among the agencies to which courts most often deferred); Nicholas R. Bednar & Kristin E. Hickman, *Chevron's Inevitability*, 85 GEO. WASH. L. REV. 1392, 1397–98 (2017) (“though the Court's rhetoric regarding *Chevron*'s scope and operation continues to evolve, we believe that reports of the doctrine's pending demise are overblown”); William N. Eskridge, Jr. & Lauren E. Baer, *The Continuum of Deference: Supreme Court Treatment of Agency Statutory Interpretations from Chevron to Hamdan*, 96 GEO L.J. 1083, 1120 (2008) (“the Court was highly deferential to agency interpretations *before* *Chevron*”); David Zaring, *Reasonable Agencies*, 96 VA. L. REV. 135, 143 (2010) (“courts tend to reverse agencies at the same rate regardless of the standard of review they apply”).

⁷⁹ For a discussion of how the risks of off-label uses may affect the FDA’s regulatory decision-making with respect to the on-label use, see Patricia J. Zettler, *The Indirect Consequences of Expanded Off-Label Promotion*, 78 OHIO STATE L.J. 1053 (2017).

⁸⁰ *See, e.g.*, Richard A. Merrill, *The Architecture of Government Regulation of Medical Products*, 82 VA. L. REV. 1753, 1826 (1996) (explaining that the FDA’s position is that the “fundamental principles underlying evaluation of any therapeutic intervention, whether it is a drug [or a] device . . . are the same”).

dosage form.⁸¹ At the same time that the FDA authorizes a product—or more precisely, a particular use for the product—it also authorizes labeling that describes that use.⁸² In this way, the manufacturer’s intentions determine the focus of the FDA’s premarket authorization decision for a particular product, as well as the scope of the labeling that the FDA authorizes for the product.

This limited scope of FDA authorization, however, frequently does not restrict how authorized products are used in medical practice.⁸³ Consistent with the conventional view that states are the primary regulators of medical practice, it has long been the FDA’s position that health care providers generally may prescribe or administer a legally marketed product for any use, including “off-label” uses that the FDA has not authorized.⁸⁴ At the same time, the FDA has long interpreted the FDCA as prohibiting manufacturers from promoting their products for off-label uses.⁸⁵ Although

⁸¹ See, e.g., FDA MEMO, *supra* note 27 at 2-3; see also Nathan Cortez, *The Statutory Case Against Off-Label Promotion*, 83 U. CHI. L. REV. ONLINE 124, 126 (2016).

⁸² See, e.g., Erika Lietzan, *The Drug Innovation Paradox*, 83 MO. L. REV. (forthcoming 2018); see also Sam F. Halabi, *The Drug Repurposing Ecosystem: Intellectual Property, Incentives, Market Exclusivity, and the Future of “New” Medicines*, 20 YALE J.L. & TECH. 1 (2018).

⁸³ See, e.g., Legal Status of Approved Labeling for Prescription Drugs; Prescribing for Uses Unapproved by the FDA, 37 Fed. Reg. 16,503, 16,504 (proposed Aug. 15, 1972). There, however, are instances in which off-label prescribing is prohibited or limited by FDA requirements (or state or Drug Enforcement Administration requirements). For example, the FDCA prohibits off-label prescribing of Human Growth Hormone (HGH). 21 U.S.C. § 333(e). The FDA also has the authority to require risk mitigation programs, known as REMS, for drugs and special controls and restrictions for devices, all of which can have the effect of limiting health care providers’ ability to prescribe drugs off-label. See, e.g., 21 U.S.C. §§ 355-1, 396.

⁸⁴ See, e.g., 21 U.S.C. § 396; FDA MEMO, *supra* note 27.

⁸⁵ See, e.g., Cortez, *supra* note 81; FDA MEMO, *supra* note 27. The FDCA does not expressly prohibit the promotion of unauthorized uses—known as “off-label” uses. Instead, the FDCA prohibits marketing in interstate commerce misbranded, adulterated, or unauthorized new drugs and devices. And, under the FDA’s interpretation of the FDCA, when manufacturer promotes an FDA-authorized drug or device for an unauthorized use, that leads to violations of the FDCA by causing a drug to be misbranded (or, in some cases, an unapproved new drug), and a device to be misbranded or adulterated. For just a small selection of articles on the FDA’s policies on off-label promotion, see Joshua M. Sharfstein & Alta Charo, *The Promotion of Medical Products in the 21st Century: Off-Label Marketing and First Amendment Concerns*, 314 JAMA 1795, 1796 (2015); Cynthia M. Ho, *First Amendment Overprotection of ‘Alternative Facts’: The Case of Cognitive Biases with Pharmaceutical Marketing*, 94 IND. L.J. (forthcoming 2019), https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3152645; Ralph F. Hall & Robert J. Berlin, *When You Have A Hammer Everything Looks Like A Nail: Misapplication of the False Claims Act to Off-Label Promotion*, 61 FOOD & DRUG L.J. 653 (2006); Ralph F. Hall & Elizabeth S. Sobotka, *Inconsistent Government Policies: Why FDA Off-Label Regulation Cannot Survive First Amendment Review Under Greater New Orleans*, 62 FOOD & DRUG

the FDA is currently reconsidering its policies on off-label promotion—which have been controversial and subject to legal challenges grounded in the First Amendment—the FDA has yet to formally change its approach to off-label promotion.⁸⁶ This means that manufacturers that wish to promote non-therapeutic uses of drugs and devices generally must first obtain FDA authorization for those uses.

Despite these limitations on marketing, off-label uses, including certain well-known non-therapeutic uses, are common.⁸⁷ For example, student use of Adderall (amphetamine aspartate), Ritalin (methylphenidate hydrochloride), and Provigil (modafinil) to improve academic performance has long been a high-profile, and controversial, example of performance-enhancing drug use.⁸⁸ All of these drugs, however, are approved for other, therapeutic uses—Adderall for attention deficit hyperactivity disorder (ADHD) and narcolepsy, Ritalin for ADHD, and Provigil for narcolepsy and other sleep disorders.⁸⁹ This means that the well-known performance-

L.J. 1 (2007); Jeffrey Chasnow & Geoffrey Levitt, *Off-Label Communications: The Prodigal Returns*, 73 FOOD & DRUG L.J. 257 (2018); Coleen Klasmeier & Martin H. Redish, *Off-Label Prescription Advertising, the FDA and the First Amendment: A Study in the Values of Commercial Speech Protection*, 37 AM. J.L. & MED. 315, 317 (2011); Joan H. Krause, *Truth, Falsity, and Fraud: Off-Label Drug Settlements and the Future of the Civil False Claims Act*, 71 FOOD & DRUG L.J. 401, 404 (2016); Aaron S. Kesselheim & Michelle M. Mello, *Prospects for Regulation of Off-Label Drug Promotion in an Era of Expanding Commercial Speech Protection*, 92 N.C. L. REV. 1539, 1542 (2014); Alan Bennett et al., *Back to First Principles: A New Model for the Regulation of Drug Promotion*, 2 J.L. & BIOSCIS. 168, 170 (2015); Ryan Abbott & Ian Ayres, *Evidence and Extrapolation: Mechanisms for Regulating Off-Label Uses of Drugs and Devices*, 64 DUKE L.J. 377, 382 (2014); David Orentlicher, *Off-Label Drug Marketing, the First Amendment, and Federalism*, 50 WASH. U. J.L. & POL'Y 89, 92 (2016); Christopher Robertson, *When Truth Cannot Be Presumed: The Regulation of Drug Promotion Under an Expanding First Amendment*, 94 B.U. L. REV. 545, 554–55 (2014); Christopher Robertson, *The Tip of the Iceberg: A First Amendment Right to Promote Drugs Off-Label*, 78 OHIO ST. L.J. 1019 (2017); Robertson & Laurion, *Tip of the Iceberg II*, *supra* note 27; John Kamp, Daniel E. Troy & Elizabeth Alexander, *FDA Marketing v. First Amendment: Washington Legal Foundation Legal Challenges to Off-Label Policies May Force Unprecedented Changes at FDA*, 54 FOOD & DRUG L.J. 555 (1999); Zettler, *Indirect Consequences*, *supra* note 112.

⁸⁶ See, e.g., FDA MEMO, *supra* note 27.

⁸⁷ Cf. Tewodros Eguale, et al., *Drug, Patient, and Physician Characteristics Associated with Off-Label Prescribing in Primary Care*, 172 ARCHIVES INTERNAL MED. 781, 781 (2012) (describing the prevalence of therapeutic off-label use); Tewodros Eguale, et al., *Association of Off-Label Drug Use and Adverse Drug Events in an Adult Population*, 176 JAMA INTERNAL MED. 55, 60 (2016) (same).

⁸⁸ See, e.g., Greely et al., *Towards Responsible Use of Cognitive-Enhancing Drugs*, *supra* note 38; PRESIDENTIAL COMMISSION FOR THE STUDY OF BIOETHICAL ISSUES, GRAY MATTERS, *supra* note 38.

⁸⁹ See Adderall Labeling, https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/011522s043lbl.pdf; Provigil Labeling,

enhancing uses of these drugs are ones that the FDA has not evaluated.

II. THE FDA’S APPROACH TO EVALUATING NON-THERAPEUTIC USES

Taken together, the limits of the drug and device definitions and the availability of off-label uses means that many non-therapeutic uses are not subject to the FDA’s drug and device premarket review authorities. But for those non-therapeutic uses that fall within those authorities—or reasonably could—the agency must decide how, and whether, to implement its gatekeeping role. This Part examines examples of how the FDA has applied its drug and device premarket review authorities to non-therapeutic uses to reveal the approach that the agency has chosen for non-therapeutic uses.

A. Approval

The FDA’s role in approving drugs and devices is, perhaps, its most-well-known and clear gatekeeping role. For drugs, this approval authority applies to “new drugs” that are not “generally recognized . . . as safe and effective,” including in the FDA’s view most, if not all, prescription drugs as well as certain over-the-counter (OTC) drugs.⁹⁰ Devices undergo more varied forms of premarket review than drugs do, with the type of review typically depending on the level of risk posed by a device and its novelty.⁹¹

https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/020717s037s038lbl.pdf;

Ritalin

Labeling,

https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/021284s034lbl.pdf.

One of Provigil’s approved indications is for excessive sleepiness associated with “shift work disorder.” Characterizing the negative circadian rhythm effects of shift work as a disorder is an example of what some commentators have criticized as the medicalization of the problems of ordinary life (or the medicalization of a problem that may be best fixed through non-medical means, such as more humane workplace policies). See, e.g., Robert Meadows et al., *The Sociology of Sleep*, in SLEEP, HEALTH, AND SOCIETY: FROM AETIOLOGY TO PUBLIC HEALTH (eds. Francesco P. Cappuccio et al., 2018).

⁹⁰ 21 U.S.C §§ 321(p); 331(d); 355(a). General recognition of safety and effectiveness is a high bar to clear. It requires at least as much evidence of safety and effectiveness as FDA approval does. See *Weinberger v. Hynson, Wescott & Dunning, Inc.*, 412 U.S. 609 (1973). In addition, to fall outside of the definition of a “new drug” a drug must have been marketed to a material extent and for a material time—which the FDA generally interprets to mean that the drug has been legally marketed in sufficient quantities, for example in another country, for at least 5 years. See, e.g., FDA, GUIDANCE FOR INDUSTRY: TIME AND EXTENT APPLICATIONS FOR NONPRESCRIPTION DRUG PRODUCTS (Sept. 2011).

⁹¹ See, e.g., Merrill, *supra* note 80; W. Nicholson Price II, *Regulating Black-Box Medicine*, 116 MICH. L. REV. 421, 438 (2017).

The highest risk, “class III” devices—such as pacemakers and implanted brain stimulators—typically require FDA approval.⁹²

Although the precise language of the statutory standards for approving new drugs under a “new drug application (NDA)” and devices under a premarket approval application (PMA) differ,⁹³ the general idea is the same: to approve a use of new drug or device, the FDA must determine that the product is safe and effective for its proposed indication and that the proposed labeling is not false or misleading.⁹⁴ The FDCA requires that the drug or device manufacturer submit to the FDA numerous kinds of information showing that this approval standard is met, which typically consists of data from one or two clinical trials.⁹⁵ Because drugs and devices cannot be perfectly safe nor equally effective for all users, “safe and effective” generally means that the benefits of the product’s intended use outweigh its risks.⁹⁶ Once a drug or device is approved the FDA’s weighing of its risks and benefits does not end. The FDA also has the authority to withdraw its approval if, among other reasons, the agency determines that the benefits of the product’s no longer outweigh its risks—for example,

⁹² 21 U.S.C. §§ 360c, 360e.

⁹³ Compare 21 U.S.C. § 355(d) with 21 U.S.C. § 360e(d). Specifically, the drug approval standard requires “adequate tests” to show the drug is safe and “substantial evidence” of effectiveness, demonstrated through “adequate and well-controlled investigations.” The device approval standard requires “reasonable assurance” of safety and effectiveness consisting of “one or more” “well-controlled investigations” or other “valid scientific evidence.” Whether these standards are the same—or instead, the device is standard is a lower one—in practice and as a statutory interpretation matter, is debated. See, e.g., Peter Barton Hutt et al., *The Standard of Evidence Required for Premarket Approval Under the Medical Device Amendments of 1976*, 47 FOOD & DRUG L.J. 605 (1992); Merrill, *supra* note 80.

⁹⁴ 21 U.S.C. § 355(d). This Article focuses on drugs approved under “new drug applications” (NDAs) pursuant to 21 U.S.C. § 355(b)(1), which are typically thought of as “brand-name” drugs. The FDA also approves generic new drugs through an abbreviated process based on evidence demonstrating a generic drug’s similarity to the relevant brand-name drug, rather than on an independent evaluation of safety and effectiveness. As with other FDA authorization processes, the abbreviated new drug application (ANDAs) process is intended to assure the safety and effectiveness of the drug. This goal, however, is accomplished by demonstrating that the generic drug is the same in all relevant respects as the brand-name drug; from that similarity, the safety and effectiveness of the generic drug can be inferred. Thus, by the time the FDA would evaluate an ANDA for a non-therapeutic use, the agency would have already made the determination most relevant to this Article—the initial determination that the non-therapeutic use is safe and effective when it approved the brand-name drug. 21 U.S.C. § 355(j); see also Eric Biber & J.B. Ruhl, *The Permit Power Revisited: The Theory and Practice of Regulatory Permits in the Administrative State*, 64 DUKE L.J. 133, 190 (2014) (describing the ANDA process as an example of the government’s permitting power).

⁹⁵ 21 U.S.C. § 355(d).

⁹⁶ See, e.g., Zettler & Lietzan, *supra* note 33.

because new risk information comes to light, as often happens once a product is used outside of the controlled clinical trial setting.⁹⁷ The following examples—although not exhaustive—demonstrate how the FDA’s has implemented these requirements for non-therapeutic uses.

1. Hair Growth Drugs

The FDA first approved drugs intended to “regrow hair on the scalp” roughly 30 years ago, when it approved Rogaine.⁹⁸ The active ingredient in Rogaine, minoxidil, was already approved at the time—but for a therapeutic use (hypertension) and in a tablet, rather than topical, form.⁹⁹ It was through developing the therapeutic use of minoxidil, when subjects in clinical trials began to experience hair growth, that the manufacturer at the time, The Upjohn Company (Upjohn), came to learn that the drug may have the potential to address hair loss as well.¹⁰⁰

Presumably because the tablet form of minoxidil was associated with serious cardiovascular adverse effects and a systemic effect of the drug was not needed for hair growth,¹⁰¹ Upjohn sought to develop a topical

⁹⁷ 21 U.S.C. § 355(e); 21 U.S.C. § 360e(e); 21 C.F.R. §814.46.

⁹⁸ See Rogaine Approval History, <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=019501>. In addition to drugs approved for hair loss, there are some drugs used off-label to regrow hair. See, e.g., Mayo Clinic, Hair Loss, <https://www.mayoclinic.org/diseases-conditions/hair-loss/diagnosis-treatment/drc-20372932>. This Part focuses on drugs approved for hair loss because the focus of this section is on the FDA authorization process for non-therapeutic uses. Moreover, although hair loss can be a result of medical problems or treatments, such as low thyroid conditions or chemotherapy drugs, and in such circumstances may be viewed as a medical problem, the drugs approved for regrowing hair do not improve or prevent such hair loss according to their FDA-approved labeling. Cf. *E.E.O.C. v. United Parcel Serv., Inc.*, 141 F. Supp. 2d 1216, 1219 (D. Minn. 2001) (concluding that a health plan’s decision to exclude Propecia was unlike its decision to exclude hormonal birth control pills because Propecia is a “non-medically necessary and elective treatment[] . . . unlike the oral contraceptives prescribed to [plaintiff] as a medically necessary treatment for a serious hormonal disorder.”).

⁹⁹ See Loniten Approval History, <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=018154>; see also W. Nicholson Price II, *Making Do in Making Drugs: Innovation Policy and Pharmaceutical Manufacturing*, 55 B.C. L. REV. 491, 562 n. 229 (2014). For a discussion of how new uses for already authorized products are developed, see Erika Lietzan, *Paper Promises for Drug Innovation*, 25 GEO. MASON L. REV. (forthcoming 2018).

¹⁰⁰ See, e.g., *Upjohn Co. v. Riahom Corp.*, 641 F. Supp. 1209, 1212 (D. Del. 1986) (describing some of the history of Upjohn’s efforts to develop Rogaine).

¹⁰¹ See Loniten Labeling, https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/018154s026lbl.pdf.

version.¹⁰² Upjohn spent three years conducting clinical trials, which ultimately showed that 26% of men using the original formulation reported “moderate to dense hair regrowth” at 4 months, compared to 11% in the placebo groups.¹⁰³ In studies of women taking the drug, 19% reported moderate hair growth at 8 months, compared to 7% in the placebo group.¹⁰⁴

Although those numbers do not seem particularly impressive, the risks associated with the topical version of minoxidil—scalp irritation being the most common one—are not particularly serious.¹⁰⁵ And the FDA determined that the benefits of topical minoxidil outweighed its risks, ultimately approving the drug to regrow hair on the scalp in 1988 for men and 1991 for women, as a prescription drug.¹⁰⁶ Likely partly because of its relatively minor risks, the FDA approved an application to switch Rogaine to over-the-counter status in 1996.¹⁰⁷

The FDA originally approved the other leading hair regrowth drug—a tablet called Propecia—in 1997.¹⁰⁸ As with Rogaine, the active ingredient in Propecia, finasteride, had been previously approved for a therapeutic use: for the treatment of symptomatic benign prostatic hyperplasia in men with enlarged prostates.¹⁰⁹ The therapeutic version of finasteride, however, was

¹⁰² See, e.g., *Upjohn*, 641 F. Supp. at 1212.

¹⁰³ See, e.g., 2005 Rogaine Labeling, https://www.accessdata.fda.gov/drugsatfda_docs/label/2005/019501s020.0251bl.pdf; see also *Upjohn*, 641 F. Supp. at 1212 (describing the time and money that Upjohn spent on developing Rogaine). Since the original formulation was approved, a stronger formulation has been approved for which studies have shown increased effectiveness. See, e.g., Men’s Extra Strength Rogaine Labeling, https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/020834Orig1s0141bl.pdf.

¹⁰⁴ See, e.g., 2005 Rogaine Labeling, *supra* note 103.

¹⁰⁵ See, e.g., *id.*

¹⁰⁶ See, e.g., Will Lester, *Hair-raising tale: no fame for men who discovered Rogaine*, THE DAILY GAZETTE, (May 13, 1996), <https://news.google.com/newspapers?id=dT5GAAAIBAJ&sjid=QukMAAAIBAJ&pg=1622%2C3318023>

¹⁰⁷ See Rogaine Approval History, <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=019501>. After switching the original formulation to OTC status, the manufacturer sought, and obtained, approval of a higher strength formulation in 1997. Again, the higher strength formulation was initially approved as a prescription drug, and then later switched to OTC status. For a discussion of some of the business reasons that manufacturers may follow this pattern of first marketing a drug as a prescription-only, and later requesting a switch to OTC status, see, e.g., [cite].

¹⁰⁸ See Propecia Approval History, <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=BasicSearch.process>.

¹⁰⁹ See Proscar Approval History, <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=020180>; Lars Noah, *This Is Your Products Liability Restatement on Drugs*, 74 BROOK. L. REV. 839, 875 (2009). A third drug, dutasteride, was approved shortly after finasteride

approved as a tablet with a dosage five-times higher than was needed for the hair growth indication.¹¹⁰ Perhaps partly for this reason, finasteride's manufacturer, Merck, sought approval of the lower dose Propecia for hair growth in men.¹¹¹

Propecia's effectiveness was demonstrated in three randomized, controlled, blinded clinical trials of men with moderate to mild hair loss, with primary endpoints of both subjects' self-assessments and hair counts.¹¹² The trials showed that men using Propecia were rated as having significantly more hair on both measures than were the men using the placebo—for example, at 12 months, 65% of men using Propecia were rated as having increased growth compared to 37% of men in the placebo group.¹¹³ Although seemingly more effective than Rogaine, Propecia also is associated with more significant risks. At the time of its original approval, the drug was known to be associated with risks to male fetuses if taken by pregnant women and with effects on Prostate-Specific Antigen levels, which are used to screen for prostate cancer risks.¹¹⁴ In 2011, it became known that the drug is also associated with an increased risk of high-grade prostate cancer.¹¹⁵ Despite these risks the FDA approved, and has not moved to withdraw its approval of, finasteride for hair loss—instead choosing to mitigate the risks through approving the drug only for men and including warnings in the FDA-approved labeling.¹¹⁶

In addition to the differences in the formulations between the therapeutic and non-therapeutic versions of minoxidil (Rogaine's active ingredient) and finasteride (Propecia's active ingredient), the manufacturers

for a similar therapeutic purpose. Although studies have suggested dutasteride may be effective for hair growth in men, it is not approved for that indication. *See, e.g.,* Avodart Approval History, <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=021319>; *see also* EA Olson et al., *The importance of dual 5alpha-reductase inhibition in the treatment of male pattern hair loss: results of a randomized placebo-controlled study of dutasteride versus finasteride*, 55 J. AM. ACAD. DERMATOLOGY 1014 (2006).

¹¹⁰ *See, e.g.,* Noah, *This is Your Products Liability Restatement on Drugs*, *supra* note 109 at 875 (describing the history of Propecia's development and noting the risks associated pill splitting).

¹¹¹ The higher dose of finasteride is associated with an increased risk of breast cancer in men, for example, while the lower dose is not known to be. *See, e.g.,* Steve T. Bird et al., *Male Breast Cancer and Finasteride and Dutasteride*, 190 J. UROLOGY 1811 (2013).

¹¹² *See, e.g.,* Propecia Labeling, https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/020788s024lbl.pdf.

¹¹³ *See id.* (p<.001).

¹¹⁴ *See* Propecia Reviews, https://www.accessdata.fda.gov/drugsatfda_docs/nda/97/020788_propecia_toc.cfm.

¹¹⁵ *See, e.g.,* June 2011 Propecia Labeling, https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020788Orig1s022lbl.pdf.

¹¹⁶ *See, e.g.,* Propecia Labeling, *supra* note 112.

may have sought approval of hair loss indications—rather than simply relying on off-label use—because they wanted to promote those indications. Rogaine’s initial approval in 1988 came shortly after the FDA’s approach to direct-to-consumer (DTC) advertising became more permissive.¹¹⁷ Upjohn began one of the pharmaceutical industry’s first disease awareness advertising campaigns directly to consumers.¹¹⁸ These campaigns featured individuals describing the “problems” associated with hair loss (e.g., “Can an emerging bald spot . . . damage your ability to get along with others, influence your chances of obtaining a job or a date or even interfere with your job performance?”) and suggested that consumers talk with their physicians.¹¹⁹ Upjohn’s campaign worked—Rogaine became a widely sold drug, with global revenue estimated at 1.2 billion dollars in 2015.¹²⁰ Likewise, Propecia was widely and successfully promoted DTC, becoming the second most highly promoted DTC drug within just a few years of approval and reaching roughly 400 million dollars in sales per year before its patent terms expired.¹²¹

2. Botox

Botox (onabotulinumtoxinA), similar to Rogaine and Propecia, was originally approved as a prescription drug for therapeutic uses—specifically for treating adult eye muscle movement disorders.¹²² After over ten years on

¹¹⁷ 56 Fed. Reg. 36,677 (1985); *see also* Wayne L. Pines, A History and Perspective on Direct-to-Consumer Promotion, 54 FOOD & DRUG L.J. 489, 493 (1999).

¹¹⁸ Jon D. Hanson & Douglas A. Kysar, *Taking Behavioralism Seriously: Some Evidence of Market Manipulation*, 112 HARV. L. REV. 1420, 1456 (1999); *see also* Lars Noah, *Advertising Prescription Drugs to Consumers: Assessing the Regulatory and Liability Issues*, 32 GA. L. REV. 141, 142 n.4 (1997); Joshua E. Perry et al., *Direct-to-Consumer Drug Advertisements and the Informed Patient: A Legal, Ethical, and Content Analysis*, 50 AM. BUS. L.J. 729, 778 n.96 (2013).

¹¹⁹ Teresa Moran Schwartz, *Consumer-Directed Prescription Drug Advertising and the Learned Intermediary Rule*, 46 FOOD DRUG COSM. L.J. 829, 837 (1991). A different advertisement for Rogaine featured a woman explaining, “I know that a man who can afford Rogaine is a man who can afford me.” *Id.*

¹²⁰ Global Market Insights, Minoxidil Market Insights, <https://www.gminsights.com/industry-analysis/minoxidil-market>.

¹²¹ *See, e.g.*, Pines, *supra* note 117 at 507-508; Jim Edwards, *Why Merck’s Hair Loss Drug Could Make Its Income Statement Go, Um, Limp*, CBSNEWS (Jan. 13, 2011), <https://www.cbsnews.com/news/why-mercks-hair-loss-drug-could-make-its-income-statement-go-um-limp/>.

¹²² *See* U.S. Food & Drug Admin., Botox Approval History, <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=103000>. Botox is a biological product, approved under a “Biologics License Application” under the Public Health Service Act.

the market as an approved therapy,¹²³ in 2002 the FDA approved Botox, under the brand-name “Botox Cosmetic,” for “the temporary improvement in the appearance of moderate to severe glabellar lines.”¹²⁴ That is, the FDA approved Botox for frown lines between the eyebrows. Although the indication on the FDA-approved labeling does not use therapeutic terms, in the approval letter, the agency described the approved use as the “*treatment* of glabellar lines” (emphasis added).¹²⁵

Botox’s use for this purpose is fairly intuitive—it is a neurotoxin that blocks nerve signals telling muscles to move, and muscle contractions are what cause wrinkles.¹²⁶ And, in fact, the FDA’s 2002 approval of Botox for glabellar lines was supported by seemingly robust evidence of effectiveness. Allergan,¹²⁷ Botox’s manufacturer, conducted two randomized, double-blind, placebo controlled clinical trials, including a total of 537 subjects with moderate to severe frown lines.¹²⁸ The subjects were injected with Botox Cosmetic and rated 30 days later—by themselves and the researchers—on the severity of their wrinkles.¹²⁹ Significantly more subjects who received Botox Cosmetic were rated as having no or only mild lines at 30 days (roughly 80% versus 3%).¹³⁰

As a neurotoxin, however, Botox is also associated with serious risks. At the time that the FDA first approved Botox for wrinkles, its FDA approved labeling including warnings about rare cardiovascular adverse events, including potentially fatal ones, as well as the transmission of viral diseases such as Creutzfeld-Jakob disease (CJD), a degenerative, fatal brain disorder.¹³¹ Since that original approval, additional risks have become

¹²³ Following its original approval, the FDA approved Botox for additional therapeutic uses, including cervical dystonia in 2000, and after Botox Cosmetic’s approval, severe primary axillary hyperhidrosis in 2004, upper limb spasticity and the prevention of headaches in patients with chronic migraines in 2010, urinary incontinence in 2011, overactive bladder in 2013, and lower limb spasticity in 2016. *See* Botox Approval History, *supra* note 122.

¹²⁴ 2002 Botox Labeling,
https://www.accessdata.fda.gov/drugsatfda_docs/label/2002/botual041202LB.pdf.

¹²⁵ 2002 Botox Cosmetic Approval Letter,
https://www.accessdata.fda.gov/drugsatfda_docs/applletter/2002/botual041202L.htm.

¹²⁶ *See, e.g., id.*

¹²⁷ Allergan is the manufacturer of many other “aesthetic” drugs and devices, including Kybella and a dermal filler marketed as Juvederm, discussed in Parts II.A.3. and II.A.5. *infra*, as well as others not discussed in detail in this Article, such as Latisse, a prescription drug approved for eyelash growth. *See, e.g.,* @megtirrell, Twitter (Sept. 14, 2018, 6:21 AM), <https://twitter.com/megtirrell/status/1040591280206749696> (<https://perma.cc/6TJB-F37R>) (describing Allergan’s “medical aesthetics day”).

¹²⁸ *See id.* Frown lines were judged moderate to severe at “maximum frown.” *Id.*

¹²⁹ *Id.*

¹³⁰ *Id.* (noting $p < .001$).

¹³¹ 2002 Botox Labeling, *supra* note 124.

known—including that Botox may spread from the site of injection to other areas of the body, producing symptoms of botulism, such as breathing difficulties, that are potentially fatal.¹³² Botox’s labeling now has a “black box warning” about this risk—the kind of warning that the FDA reserves for the most serious risks.¹³³ None of the risks of Botox, however—including the potentially fatal ones—have led the FDA to decline to approve, or withdraw approval of, the use of Botox for glabellar lines.

Moreover, these risks did not lead the FDA to decline to approve two additional non-therapeutic uses for Botox—lateral canthal lines (*i.e.*, crow’s feet) in 2013 and forehead lines in 2017—for which there was effectiveness data similar to that for glabellar lines.¹³⁴ Although physicians (and other health care providers) could, and undoubtedly did, provide Botox for these purposes before the FDA approvals, Allergan, nevertheless, undertook the clinical trials necessary to assess the drug’s safety and effectiveness for these uses, as well as to obtain the FDA’s approval.¹³⁵ That investment—as well as DTC advertising campaigns, which recently have begun to target men as well as women—has paid off.¹³⁶ By 2006, yearly sales of Botox were over 1 billion dollars with approximately half due to cosmetic uses.¹³⁷ By 2013, yearly sales were over 2 billion dollars and the continued research and development of new uses of Botox were identified as a driver of

¹³² See, e.g., 2009 Botox Labeling, https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/103000s5109s5210lbl.pdf.

¹³³ See, e.g., 21 C.F.R. § 201.57(c); U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: WARNINGS AND PRECAUTIONS, CONTRAINDICATIONS, AND BOXED WARNING SECTIONS OF LABELING (2011).

¹³⁴ 2013 Botox Approval Letter, https://www.accessdata.fda.gov/drugsatfda_docs/applletter/2013/103000Orig1s5260ltr.pdf; 2017 Botox Approval Letter, https://www.accessdata.fda.gov/drugsatfda_docs/applletter/2017/103000Orig1s5303ltr.pdf.

¹³⁵ Allergan is one of the companies that has challenged the FDA’s policies on off-label promotion on First Amendment grounds, although Allergan withdrew its lawsuit as part of a separate settlement. See, e.g., Complaint, *Allergan v. FDA*, No. 1:09-cv-01879-JDB (D.D.C. Jan. 11, 2010); Margaret Gilhooley, *Commercial Speech and Off-Label Drug Uses: What Role for Wide Acceptance, General Recognition and Research Incentives?*, 37 AM. J.L. & MED. 258, 269 (2011); Gerald Masoudi & Christopher Pruitt, *The Food and Drug Administration v. the First Amendment: A Survey of Recent FDA Enforcement*, 21 HEALTH MATRIX 111, 128 (2011).

¹³⁶ See, e.g., Al Ries, *What Botox and Viagra Teach Us About Advertising*, AD AGE (Feb. 17, 2003), <http://adage.com/article/viewpoint/botox-viagra-teach-advertising/36856/>; Aliko Carter, *Deion Sanders Loves BOTOX and is Getting His Message Out to Men*, FORBES (Jan. 15, 2018), <https://www.forbes.com/sites/alikocarter/2018/01/15/deion-sanders-loves-botox-and-is-getting-his-message-out-to-men/#2ad45d055234>.

¹³⁷ See, e.g., Emilia Petrarca, *On the 15th Anniversary of Botox, An Appreciation of How It’s Changed Everything*, W MAGAZINE (Apr. 14, 2017), <https://www.wmagazine.com/story/botox-anniversary-kim-kardashian-joan-rivers>.

Allergan's value.¹³⁸

3. Kybella

Kybella (deoxycholic acid)—originally approved as a prescription drug in 2015 for the “improvement in the appearance of moderate to severe convexity or fullness associated with submental fat in adults (*i.e.*, “double chin”)—offers a third example of an approved non-therapeutic use of a drug.¹³⁹ Unlike the previous examples, Kybella was not discovered through therapeutic use.¹⁴⁰ Instead, the idea of dissolving fat through chemical injections dates back to European practices in the 1950s and 60s.¹⁴¹

As with previous examples, Kybella's manufacturer (originally Kythera BioPharmaceuticals, now Allergan) conducted clinical trials to establish Kybella's effectiveness.¹⁴² In two randomized, placebo-controlled, blinded trials 70% of subjects who received Kybella were judged—by investigators and themselves—to have a reduction in fat volume, compared to roughly 19% in the control group.¹⁴³ Kybella, like all drugs, is not risk free. It is associated with serious risks including facial nerve injury, difficulty swallowing, and necrosis at the injection site, among other things.¹⁴⁴ None of these risks have merited a black box warning, like Botox has, however—nor, of course, have they led the FDA to conclude that the benefits of Kybella do not outweigh its risks.¹⁴⁵ Similar to other approved non-therapeutic uses of drugs, Kybella has been the subject of DTC advertising, although its sales have not been as robust as predicted.¹⁴⁶

¹³⁸ See, e.g., Joseph Walker, *Valeant, Allergan Agree on Botox's Potential*, WALL ST. J. (May 19, 2014).

¹³⁹ See Kybella Labeling, https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/206333s001lbl.pdf; cf. Lars Noah, *State Affronts to Federal Primacy in the Licensure of Pharmaceutical Products*, 2016 MICH. ST. L. REV. 1, 39 (2016) (discussing the ways that a drug like Kybella might cut into cosmetic surgeons' business).

¹⁴⁰ See, e.g., Lindsey Hunter Lopez, *The Injection That Melts a Double Chin*, THE ATLANTIC (June 14, 2017), <https://www.theatlantic.com/health/archive/2017/06/kybella-the-injection-that-melts-a-double-chin/529893/>.

¹⁴¹ See *id.*

¹⁴² See Kybella Labeling, *supra* note 139.

¹⁴³ *Id.*

¹⁴⁴ *Id.*; see also Rita Rubin, *FDA Okays Drug to Reduce Double Chins*, 313 JAMA 2115, 2115 (2015).

¹⁴⁵ Kybella Labeling, *supra* note 139.

¹⁴⁶ Carly Helfand, *Did Allergan Lose its \$2.1B Kythera Bet, or can Chin-Fat Drug Kybella Make its Mark?*, FIERCEPHARMA (Nov. 7, 2017), <https://www.fiercepharma.com/pharma/did-allergan-lose-its-2-1-kythera-bet-or-can-kybella-make-a-comeback> (reporting that Allergan revised its peak yearly sales estimates

4. Breast Implants

The FDA's regulation of breast implants—and in particular, silicone breast implants—has a long, complicated, and controversial history.¹⁴⁷ Although breast implants have been on the market since the early 1960s, Congress did not create the FDA's modern scheme for regulating devices until 1976 and the FDA did not require breast implant manufacturers to submit premarket approval applications (PMAs) until 1991.¹⁴⁸ Today there are over 200 PMAs approved for breast implants—and the overall history of breast implant approval offers a few insights into the FDA's approach for non-therapeutic uses.¹⁴⁹

The FDA approved the first PMAs for breast implants in 2000. The applications covered saline breast implants intended either for aesthetic uses or for reconstruction.¹⁵⁰ That is, the FDA approved the implants both for non-therapeutic and therapeutic uses. At the time of approval, the FDA judged the implants—whether intended for aesthetic or reconstructive purposes—to be associated with a variety of risks, including serious risks such as the likely need for additional surgery over the course of the recipient's life. The FDA, however, judged the benefits of both the aesthetic and reconstructive uses to outweigh these risks, provided certain conditions—such as conducting a 10-year post-approval follow-up study—were met.¹⁵¹

This is not to say that the agency judged the benefits of non-therapeutic uses as equal to those of therapeutic uses. For example, the aesthetic indication for the first approved breast implants was limited to adults,

for Kybella to 100 million dollars, down from 400 million dollars).

¹⁴⁷ See, e.g., MARCIA ANGELL, *SCIENCE ON TRIAL: THE CLASH OF MEDICAL EVIDENCE AND THE LAW IN THE BREAST IMPLANT CASE* (1996); Rebecca S. Dresser et al., *Breast Implants Revisited: Beyond Science on Trial*, 1997 WIS. L. REV. 705, 706 (1997); David E. Bernstein, *The Breast Implant Fiasco*, 87 CAL. L. REV. 457 (1999); U.S. Food & Drug Admin., *Regulatory History of Breast Implants in the U.S.*, <https://www.fda.gov/medicaldevices/productsandmedicalprocedures/implantsandprosthetics/breastimplants/ucm064461.htm>.

¹⁴⁸ *Regulatory History of Breast Implants*, *supra* note 147.

¹⁴⁹ A search for “breast implant” in the FDA's PMA database yields roughly 230 approved applications. U.S. Food & Drug Admin., *Premarket Approval*, <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm>.

¹⁵⁰ See, e.g., *Regulatory History of Breast Implants*, *supra* note 147. Allergan, the manufacturer of Botox, Latisse, and Kybella, was also the manufacturer of one of the first approved breast implants. See U.S. Food & Drug Admin., *Natrelle Saline Breast Implants*, <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P990074>.

¹⁵¹ See, e.g., *Natrelle Approval Order*, https://www.accessdata.fda.gov/cdrh_docs/pdf/P990074A.pdf.

whereas the indication for reconstruction was not, suggesting that the FDA may have weighed the two uses differently.¹⁵² Additionally, until 2006, the FDA authorized only the reconstructive, but not the aesthetic, use of silicone breast implants—which at the time were thought to be associated with risks greater than those associated with saline implants.¹⁵³ This different approach likely reflected the FDA’s view that those potential greater risks were outweighed by reconstructive but not aesthetic benefits.¹⁵⁴

5. Dermal Fillers

As with breast implants, the FDA—since the early 1980s—has approved as devices dozens of dermal fillers, under brand-names such as Restylane and Juvederm.¹⁵⁵ Dermal fillers typically consist of materials such as collagen or hyaluronic acid that are injected into the body to smooth wrinkles or add volume to the skin.¹⁵⁶ Although dermal fillers are injectable products, they are devices, rather than drugs, because they work through physically filling the skin rather than through chemical action.¹⁵⁷

Like many of the non-therapeutic uses of drugs, the FDA determined that at least some dermal fillers are effective based on clinical trials assessing both investigators’ and subjects’ own judgments that the dermal fillers had reduced the appearance of wrinkles.¹⁵⁸ Also like both breast implants and non-therapeutic uses of drugs, dermal fillers are not risk-free. The most common adverse events are relatively minor, including bruising,

¹⁵² See U.S. Food & Drug Admin., Summary of Safety and Effectiveness Data, Saline-Filled Mammary Prosthesis, https://www.accessdata.fda.gov/cdrh_docs/pdf/P990074B.pdf.

¹⁵³ FDA, Regulatory History of Breast Implants, *supra* note 147; see also Mehlman, *supra* note 10. The concerns about silicone breast implants being associated with, for example, autoimmune disorders were ultimately not borne out, notwithstanding arguments made in tort lawsuits against the manufacturers. See, e.g., Dresser et al., *supra* note 147; Bernstein, *supra* note 147.

¹⁵⁴ See Mehlman, *supra* note 10.

¹⁵⁵ A search for “dermal filler” in the FDA’s PMA database yields 64 approved applications. U.S. Food & Drug Admin., Premarket Approval, <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm>.

¹⁵⁶ See, e.g., Restylane Labeling, https://www.accessdata.fda.gov/cdrh_docs/pdf14/P140029C.pdf; U.S. Food & Drug Admin., Dermal Fillers Approved by the Center for Devices and Radiological Health, <https://www.fda.gov/medicaldevices/productsandmedicalprocedures/cosmeticdevices/wrinklefillers/ucm227749.htm>.

¹⁵⁷ 21 U.S.C. § 321(g)(1), (h); see also Lars Noah, *Growing Organs in the Lab: Tissue Engineers Confront Institutional “Immune” Responses*, 55 JURIMETRICS J. 297, 338 n.93 (2015).

¹⁵⁸ See, e.g., Restylane Labeling, https://www.accessdata.fda.gov/cdrh_docs/pdf14/P140029C.pdf.

pain, and redness.¹⁵⁹ They, also, however are associated with serious adverse effects—including health-related effects, such as necrosis and anaphylactic shock, as well as aesthetic effects, such as movement of the filler or the formation of permanent, hard nodules on the skin.¹⁶⁰ Consistent with these risks, the FDA restricts dermal fillers to prescription use.¹⁶¹

B. Other Routes to Market through the FDA

Certain uses of drugs and devices are subject to FDA requirements that differ from the approval requirements described above. Perhaps this most important example is that most devices do not undergo the rigorous PMA review process.¹⁶² Instead, manufacturers of moderate risk devices—those in class II—typically obtain FDA “clearance” for marketing their devices, rather than premarket approval, by demonstrating that a device is “substantially equivalent” to a device already on the market.¹⁶³ That is, instead of demonstrating that the device is safe and effective, the manufacturer demonstrates that the device has the same intended use and the same technological characteristics as a “predicate device”—which allows the FDA to infer that the new device is as safe and effective as the currently marketed one.¹⁶⁴

As with FDA approval, this clearance process—known as the 510(k) process, named after the relevant statutory provision—also has been used to authorize the marketing of certain non-therapeutic uses.¹⁶⁵ The FDA’s

¹⁵⁹ U.S. Food & Drug Admin., Dermal Fillers (Soft Tissue), <https://www.fda.gov/MedicalDevices/ucm2007470.htm>.

¹⁶⁰ *See, e.g., id.*

¹⁶¹ *See, e.g., Restylane Approval Order*, https://www.accessdata.fda.gov/cdrh_docs/pdf14/P140029A.pdf.

¹⁶² *See, e.g., GAO, MEDICAL DEVICES: FDA SHOULD TAKE STEPS TO ENSURE THAT HIGH-RISK DEVICE TYPES ARE APPROVED THROUGH THE MOST STRINGENT PREMARKET REVIEW PROCESS (GAO-09-190) (2009).*

¹⁶³ 21 U.S.C. § 360(k); Hall & Mercer, *supra* note 31. The lowest risk, “class I” devices—products like band-aids and tongue depressors—are typically not subject to any premarket review.

¹⁶⁴ 21 U.S.C. § 360(k).

¹⁶⁵ It is also possible that novel non-therapeutic uses of devices that lack a suitable predicate and pose moderate or low risks might reach the market through the “de novo” review process. Under this process, instead of seeking approval through the PMA process, manufacturers provide FDA with data and information sufficient for the agency to determine that the device is low or moderate risk. 21 U.S.C. § 360c(f); FDA, GUIDANCE FOR INDUSTRY AND FDA STAFF: DE NOVO CLASSIFICATION PROCESS (Oct. 2017). Thus far the de novo process does not appear to have been used for non-therapeutic uses. It may, however, be used in the future, for example for non-invasive brain stimulation devices marketed for performance enhancement, which some researchers have suggested may be

approach to clearing non-therapeutic uses under a 510(k) does not seem appreciably different than its approach to approving non-therapeutic uses under a PMA (or NDA). For example, the FDA has authorized the marketing of decorative contact lenses both pursuant to PMAs and 510(k)s.¹⁶⁶ Although decorative lenses pose the same risks as corrective lenses—including serious risks, such as injuries and infections that can lead to blindness—the FDA seems to “make[] no regulatory distinction between contact lenses for corrective versus cosmetic use,” permitting manufacturers to market decorative lenses “under the same conditions as corrective lenses, despite the argument that, given the risks from contact lens use, the ratio of risks to benefits ought to be more favorable to justify the use of lenses for purely cosmetic purposes.”¹⁶⁷ The FDA is more limited in its review of 510(k) submissions. It is, after all, assessing a product’s similarity to a predicate device rather than its safety and effectiveness.¹⁶⁸ Nonetheless, FDA arguably could have created different requirements—or assessed 510(k)s differently—for decorative and corrective lens on the ground that the decorative use raises new types of safety and effectiveness questions.¹⁶⁹

Another example of an FDA process for weighing the safety and effectiveness of a non-therapeutic use outside of the approval processes comes from OTC drugs. Most OTC are marketed without FDA approval, not because the agency is exercising enforcement discretion, but because the agency has determined that they are do not fall within the category of “new drugs” requiring approval.¹⁷⁰ These OTC drugs are marketed pursuant to FDA regulations, known as “monographs,” that provide the

associated with minimal risks. *Cf.* Francis X. Shen, *Law and Neuroscience 2.0*, 48 ARIZ. ST. L.J. 1043, 1059 (2016) (raising questions about how this kind of technology should be regulated).

¹⁶⁶ DECORATIVE CONTACT LENS GUIDANCE, *supra* note 4. Additionally, decorative and corrective lenses are classified the same. *See, e.g.*, 21 C.F.R. § 886.5928 (declining to distinguish between decorative and corrective lenses).

¹⁶⁷ *See* Mehlman, *supra* note 10 at 702; *see also* Acuvue Brand Lenses, 510(k) Summary (Feb. 26, 2002), https://www.accessdata.fda.gov/cdrh_docs/pdf/K013973.pdf (discussing the evidence supporting authorization for both corrective and aesthetic uses).

¹⁶⁸ 21 U.S.C. § 360(k).

¹⁶⁹ *See, e.g., id.*; Hall & Mercer, *supra* note 31. Given the frequency with which the 510(k) process is used for devices, it should be unsurprising that decorative contact lenses are not the only example of an FDA-cleared non-therapeutic use. The Zetliq CoolSculpting system, intended for cold-assisted lipolysis (i.e., breaking down fat in “love handles”) offers another example of a non-therapeutic use cleared through the 510(k) process. The predicate device for Zetliq CoolSculpting is a device manufactured by the same company, which is intended to minimize pain during laser and dermatologic interventions. As with decorative lenses, the agency did not seem to conclude that the non-therapeutic uses of the device required a different approach than did the therapeutic uses. *See, e.g.*, Zetliq 510(k) Summary, May 2, 2012, https://www.accessdata.fda.gov/cdrh_docs/pdf12/K120023.pdf.

¹⁷⁰ *See, e.g.*, 79 Fed. Reg. 10168 (Feb. 24, 2014); *see also* 21 U.S.C. § 321(p), 355(a).

conditions under which an OTC drug is generally recognized as safe and effective, and not misbranded—permitting the drug to fall outside the FDA approval requirement.¹⁷¹ Although these drugs are not approved, the agency evaluated the safety and effectiveness data about particular uses of active ingredients, including some non-therapeutic uses, to issue these monographs.¹⁷²

As with the prescription drug context, many of the non-therapeutic uses that the FDA has assessed for OTC use are aesthetic uses, the non-therapeutic uses are not risk-free, and user perceptions offered evidence supporting effectiveness. For example, in 2003 based on data including evidence derived from user perception testing, the FDA determined that numerous active ingredients, such as aluminum chloride, are generally recognized as safe and effective for antiperspirant use.¹⁷³ Consistent with their status as OTC drugs, the use of these ingredients as antiperspirants is associated with relatively minor risks—such as skin irritation—although the labeling does caution that consumers with kidney disease should ask a doctor before use.¹⁷⁴

Other OTC monographs, however, cover non-therapeutic uses that do not pertain to aesthetics. For example, in 1988, the FDA concluded that caffeine, in doses roughly equivalent to a cup of coffee, was generally recognized as safe and effective as a stimulant for adults to “help[] restore mental alertness or wakefulness when experiencing fatigue or drowsiness.”¹⁷⁵ The OTC context also provides some indication that FDA is willing to decline to find a non-therapeutic use safe and effective, including in the aesthetic context. In 1990, for example, it concluded that there were not sufficient data to demonstrate that skin bleaching drugs were

¹⁷¹ See, e.g., *id.* In short, the monograph process was devised as a way to efficiently evaluate all of the nonprescription drugs being marketed in the 1960s, when Congress granted FDA authority to review drugs’ effectiveness. Peter Barton Hutt, *The State of Science at the Food and Drug Administration*, 60 ADMIN. L. REV. 431, 447 (2008).

¹⁷² See, e.g., 79 Fed. Reg. 10168.

¹⁷³ 21 C.F.R. § 350.10; 68 Fed. Reg. 34273 (June 9, 2003); Permitted indications include “decreases dampness,” “lessens perspiration,” or “reduces sweat.” *Id.* Antiperspirants are drugs because they are intended to affect the sweat function of the body through chemical action. See, e.g., HUTT ET AL., *supra* note 72 (offering antiperspirant as an example of a drug that is intended to affect the structure or function of the body).

¹⁷⁴ See *id.* The kidney disease warning is included because individuals with kidney disease cannot remove aluminum from their bodies in the same manner that individuals without kidney disease can. However, it is unlikely that much if any aluminum is absorbed through the skin through antiperspirant use. See, e.g., National Kidney Foundation, Antiperspirants, <https://www.kidney.org/atoz/content/antiperspirants>.

¹⁷⁵ 21 C.F.R. § 340.50; 53 Fed. Reg. 6100 (Feb. 29, 1988). The risks associated with using such caffeine-containing drugs are relatively non-serious, and include, according to the labeling, nervousness, irritability, and rapid heartbeat. *Id.*

generally recognized as safe and effective.¹⁷⁶ This conclusion did not mean that skin bleaching drugs could never be sold, or sold without a prescription—but instead, that FDA approval would be required.¹⁷⁷ Nevertheless, the determination suggests that the value of a non-therapeutic use is not so subjective as to wholly prevent the FDA finding an unfavorable benefit-risk balance.

C. Enforcement Discretion

Some non-therapeutic uses of drugs and devices do not go through a formal FDA assessment because the FDA has declined to enforce its requirements.¹⁷⁸ For example, in 2016 the FDA issued a guidance creating such a policy for “low risk general wellness” devices.¹⁷⁹ According to the FDA, general wellness devices include some device uses that may be non-therapeutic—such as devices intended to improve physical fitness, enhance learning capacity or mental acuity, and enhance sexual function.¹⁸⁰ The FDA’s 2016 guidance explained that the agency does not intend to enforce premarket review requirements for such uses, or even assess whether the products are devices—so long as the products are also low risk.¹⁸¹ Low risk products include those that are not implanted, not invasive, and do not require specific regulatory controls to mitigate the risks to the users.¹⁸² In other words, although the FDA’s guidance created a policy that removes the FDA’s role in weighing risks and benefits for each of the products in this group—that decision was based on an assessment that the risks associated with these products are low.¹⁸³

For other non-therapeutic uses, the agency appears to have more informally exercised its discretion not to enforce premarket review requirements. As one example, in 2015 the FDA held a public meeting at

¹⁷⁶ 55 Fed. Reg. 46914 (Nov. 7, 1990).

¹⁷⁷ See, e.g., 21 U.S.C. § 321(p), 355(a).

¹⁷⁸ See, e.g., *Heckler v. Cheney*; see also *Paradise, Regulatory Silence*, *supra* note 25; *Zaring*, *supra* note 25; cf. *Biber and Ruhl*, *supra* note 94 (discussing the range of permitting structures available to agencies).

¹⁷⁹ GENERAL WELLNESS GUIDANCE, *supra* note 25.

¹⁸⁰ See *id.* at 3. On the other, notwithstanding the enhancement examples included in the guidance, the FDA defines general well devices, generally, as intended to support health states or reduce the risk of disease, which would be therapeutic uses as defined in this Article. See *id.* at 2.

¹⁸¹ See *id.*

¹⁸² See *id.* at 5.

¹⁸³ After the FDA issued the guidance, Congress added a provision to the FDCA expressly establishing that certain general wellness software applications are not devices. See Part II.B, *supra*.

which, among other things, it requested comments on its regulation of non-invasive brain stimulation products used for performance enhancement, suggesting that the agency thinks it does—or could—have jurisdiction over such products.¹⁸⁴ The risks of these stimulation devices are not known to be particularly serious, but nor are they clearly low-risk as defined in the Wellness Guidance.¹⁸⁵ For example, it may be that special controls—such as particular warnings in consumer labeling—are needed to ensure that consumers use the devices appropriately and to mitigate the risks of skin burns.¹⁸⁶ As another example, the FDA, thus far, has focused its regulation of cannabis-containing products on those intended for medical uses.¹⁸⁷ There are likely many reasons for this—including the intersection with state and Drug Enforcement Administration (DEA) policies on cannabis.¹⁸⁸ But the FDA, if it chose to do so, likely could assert its jurisdiction over recreational cannabis-containing products, as drugs intended to affect the structure or function of the body.¹⁸⁹ Yet, although the FDA has not publicly

¹⁸⁴ Neurodiagnostics and Non-Invasive Brain Stimulation Medical Devices; Public Workshop; Request for Comments, 80 Fed. Reg. 48,869 (Aug. 14, 2015); *see also* Zettler, *tDCS*, *supra* note 9 (explaining the argument that the FDA does have jurisdiction over such products as devices).

¹⁸⁵ *See, e.g.*, Marom Bikson et al., *Safety of Transcranial Direct Current Stimulation: Evidence Based Update 2016*, 9 BRAIN STIMULATION 641 (2016); Wexler, *supra* note 71.

¹⁸⁶ *Cf.* Shen, *supra* note 165 at 1059 (asking the question of “how, if at all, the FDA should regulate this technology”); Wexler, *supra* note 71 (discussing some of the risks of tDCS devices).

¹⁸⁷ *See, e.g.*, U.S. Food & Drug Admin., FDA and Marijuana, <https://www.fda.gov/newsevents/publichealthfocus/ucm421163.htm>; *see also* Warning Letter to Stanley Brother Social Enterprises LLC (Oct. 31, 2017), <https://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2017/ucm583192.htm> (citing violations of the FDCA related to a CBD-containing product marketed as a cancer therapy).

¹⁸⁸ *See, e.g.*, William W. Buzbee, *Recognizing the Regulatory Commons: A Theory of Regulatory Gaps*, 89 IOWA L. REV. 1, 6 (2003) (“when social ills match no particular political-legal regime or jurisdiction, but instead encounter fragmented political-legal structures, predictable incentives arise for potential regulators to opt against investing in such regulatory opportunities”); *see also* Alex Kreit, *What Will Federal Marijuana Reform Look Like?*, 65 CASE W. RES. L. REV. 689, 698 (2015); Kevin A. Sabet, *Much Ado About Nothing: Why Rescheduling Won't Solve Advocates' Medical Marijuana Problem*, 58 WAYNE L. REV. 81, 101 (2012).

¹⁸⁹ *Cf.* *United States v. Storage Spaces Designated Nos. 8 & 49 Located at 277 E. Douglas, Visalia, Cal.*, 777 F.2d 1363, 1366 (9th Cir. 1985) (concluding a recreational drug is within FDA jurisdiction); *United States v. Travia*, 180 F. Supp. 2d 115, 116 (D.D.C. 2001) (same); Angela LaVito, *As Pot Stock Jumps Around, FDA Chief Says He's More Worried about Teens Using Marijuana than E-cigarettes*, CNBC (Sept. 20, 2018), <https://www.cnn.com/2018/09/20/fda-chief-gottlieb-worries-about-teens-using-marijuana.html> (reporting that the FDA Commissioner expressed concerns about the health risks that recreational cannabis use poses). For a full account of the FDA's jurisdiction over cannabis-containing products, *see* Sean O'Connor & Erika Lietzan, *The Surprising Reach*

announced a policy of enforcement discretion for either brain stimulation devices intended for enhancement or cannabis-containing products intended for recreational use, the agency so far has seemed to decline to enforce drug and device requirements, including for premarket review, for these products.¹⁹⁰

III. EVALUATING THE FDA'S APPROACH

This section considers what to make of the FDA's history of assessing non-therapeutic uses of drugs and devices. It first identifies several themes that emerge from the regulatory history, arguing that the FDA's approach to non-therapeutic uses is consistent with that for therapeutic uses. It then evaluates that approach in light of the purposes that FDA gatekeeping is thought to serve.

A. Themes in the FDA's Approach

Considering examples of how the non-therapeutic uses of drugs and devices have reached the market reveals a few themes. First, the agency does not require all non-therapeutic uses of drugs and devices that could be required to do so to undergo FDA review. As the Wellness Guidance—and perhaps the FDA's approach to enhancing uses of non-invasive brain stimulation devices—demonstrates, the agency may choose to exercise its discretion not to enforce requirements for drugs and devices within its jurisdiction, and often does so when it determines that the risks of the products are not sufficiently serious to merit regulation.¹⁹¹ This is consistent with the agency's overall risk-based approach to selecting enforcement priorities, as well as the ways in which it chooses to regulate therapeutic uses of drugs and devices.¹⁹²

of *FDA Regulation of Cannabis, Even after Descheduling*, available at https://papers.ssrn.com/sol3/cf_dev/AbsByAuth.cfm?per_id=2000555.

¹⁹⁰ See, e.g., Stacy Lawrence, *Khosla-backed Thync Dodges FDA, Heads to Market with \$299 Mood-Shifting Consumer Wearable*, FierceBiotech (June 3, 2015), <https://www.fiercebiotech.com/medical-devices/khosla-backed-thync-dodges-fda-heads-to-market-299-mood-shifting-consumer-wearable>; see also Esther Landhuis, *Do DIY Brain-Booster Devices Work?* SCI. AM. (Jan. 10, 2017), <https://www.scientificamerican.com/article/do-diy-brain-booster-devices-work/>.

¹⁹¹ See, e.g., WELLNESS GUIDANCE, *supra* note 24.

¹⁹² See, e.g., U.S. Food & Drug Admin., FDA proposes new, risk-based enforcement priorities to protect consumers from potentially harmful, unproven homeopathic drugs, <https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm589243.htm>; see also

Second, when the agency does enforce requirements for pre-market review of non-therapeutic uses of drugs and devices, its decisions have not reflected a view that the benefits of non-therapeutic uses are radically less valuable than those of therapeutic uses.¹⁹³ For example, the agency is willing to conclude that non-therapeutic uses outweigh the risks of serious risks in some instances. Breast implants can create the need for additional surgeries.¹⁹⁴ Dermal fillers are associated with a risk of anaphylactic shock as well as a risk of permanent, undesirable aesthetic affects.¹⁹⁵ The use of Propecia is associated with an increased risk, albeit a small one, of high-grade prostate cancer.¹⁹⁶ Botox is required to have a black-box warning—the warning that FDA uses for drugs with the most serious risks—describing the possibility that the drug may spread from the injection area leading to life-threatening difficulty breathing and swallowing.¹⁹⁷ For non-therapeutic uses of devices that have undergone 510(k) review—such as decorative contacts—the agency has not established different controls for the therapeutic and non-therapeutic uses of the devices.¹⁹⁸ Likewise, in the General Wellness Guidance, the agency did not announce different policies for therapeutic and non-therapeutic “wellness” uses of low-risk devices.¹⁹⁹

Another indication of the somewhat similar value placed on non-therapeutic and therapeutic uses is that the FDA has been approved certain non-therapeutic uses with evidence of relatively small effects—suggesting a large non-therapeutic benefit is not needed to outweigh any risks of the use. For example, Rogaine was approved for women when studies showed that roughly 12% more women using Rogaine, than using a placebo, experienced moderate hair growth.²⁰⁰ Additionally, that the FDA permits Rogaine—and other drugs with minimal risks, such as caffeine pills—to be marketed OTC also suggests some similarity in the way the agency views therapeutic and non-therapeutic uses.

This is not to say that the benefits of non-therapeutic uses are identical in value to those of therapeutic uses. For example, until 2006, the FDA authorized only the reconstructive, but not aesthetic use of silicone breast implants, while it had authorized both kinds of uses for saline breast

Nathan G. Cortez, et al, *FDA Regulation of Mobile Health Technologies*, 371 NEW ENG. J. MED. 372, 376 (2014).

¹⁹³ Cf. Greely, *supra* note 10 (describing non-therapeutic uses as less important than therapeutic ones); Mehlman, *supra* note 10 (same).

¹⁹⁴ See Part II, *supra*.

¹⁹⁵ See *id.*

¹⁹⁶ See *id.*

¹⁹⁷ See *id.*

¹⁹⁸ See *id.*

¹⁹⁹ See *id.*

²⁰⁰ See *id.*

implants.²⁰¹ This different approach likely reflected the FDA’s view that silicone breast implants might carry greater risks than saline implants, and that those risks were outweighed by reconstructive but not cosmetic benefits.²⁰²

Moreover, although some non-therapeutic uses are associated with serious risks, the risks have not generally warranted the agency’s most restrictive risk management programs. As one example, after the Food and Drug Administration Amendments Act of 2007 authorized the FDA to require special risk mitigation programs for prescription drugs—known as REMS—the agency required such a program for Botox. The FDA is authorized to require a REMS when necessary to ensure that a drug’s benefits outweigh its risks, meaning that REMS are reserved for prescription drugs with the most serious risks and for instances in which a REMS is necessary for the drug to meet the approval standard.²⁰³ All REMS, however, are not alike. REMS include risk management tools that range from the relatively minimal, such as dispensing patient labeling, to the relatively stringent, including restricting prescribing and dispensing to providers with special training and requiring that certain laboratory tests be documented before a patient receives a drug.²⁰⁴ The Botox REMS was among the least restrictive REMS—it primarily consisted of patient labeling—and is now no longer required.²⁰⁵ That Botox was required to have a REMS that applied to both its therapeutic and non-therapeutic uses—but a non-restrictive one—provides more evidence that the FDA views non-therapeutic uses as similar, although not identical, in value to therapeutic uses.

Third, the FDA’s review of non-therapeutic uses also demonstrates that various forms of evidence can demonstrate sufficient effectiveness. Many of the non-therapeutic uses of drugs and devices that have undergone premarket approval—such as hair loss drugs, Botox, Kybella, and dermal fillers—were determined to be effective based on trials that used subjects’ own evaluations of their appearance as one primary endpoint.²⁰⁶ This approach is consistent with a recent change to the FDCA encouraging the FDA to incorporate “patient experience data” into its evaluations.²⁰⁷

²⁰¹ FDA, Regulatory History of Breast Implants, *supra* note 9; *see also* Mehlman, *supra* note 10.

²⁰² *See* Mehlman, *supra* note 10.

²⁰³ 21 U.S.C. § 355-1.

²⁰⁴ *Id.*

²⁰⁵ *See* FDA, Approved Risk Evaluation and Mitigation Strategies (REMS), <https://www.accessdata.fda.gov/scripts/cder/remis/>.

²⁰⁶ *See* Part II, *supra*.

²⁰⁷ *See, e.g.,* Jordan Paradise, *21st Century Citizen Pharma: The FDA & Patient-Focused Product Development*, 44 AM. J.L. & MED. (forthcoming 2018),

Although concerns have been raised about incorporating subjective patient experiences into evaluating therapeutic uses of drugs and devices, particularly when patient advocacy groups are financially supported by the drug or device manufacturers,²⁰⁸ it is possible that such information may be more easily integrated into the evaluation of aesthetic uses, for which the user's satisfaction with his or her appearance is the ultimate goal.

Notably, many of the non-therapeutic uses that the FDA has evaluated have been aesthetic uses, rather than performance enhancing or recreational uses.²⁰⁹ There may be many reasons that FDA-evaluated non-therapeutic uses are currently primarily aesthetic ones. One may be that the market for aesthetic uses of products is robust, motivating manufacturers to spend the time and resources to develop the data necessary to satisfy the FDA.²¹⁰ For example, the non-therapeutic uses of Botox remain a strong source of revenue for the drug's manufacturer.²¹¹ Another possibility is that it is easier to demonstrate that a product is effective for an aesthetic use than for other non-therapeutic uses. The relatively long history of marketing of aesthetic uses of drugs and devices provides some precedent for understanding what kinds of evidence can demonstrate safety and effectiveness in this context. Aesthetic uses also may be more socially acceptable than performance-enhancing or recreational uses of drugs and devices. Whatever the reason, the dominance of aesthetic uses is important to note because it may be that the FDA would assess performance-enhancing or recreational uses differently. At least for aesthetic non-therapeutic uses, however, being subject to FDA jurisdiction need not be viewed as an insurmountable obstacle to profitable marketing.

B. The Purposes of Premarket Review

The FDA's gatekeeping function is typically described as serving at least three important purposes: protecting consumers from unsafe or ineffective products, addressing informational asymmetries between consumers and manufacturers, and incentivizing the creation of socially

https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3131857.

²⁰⁸ See, e.g., Aaron S. Kesselheim & Jerry Avorn, *Approving a Problematic Muscular Dystrophy Drug: Implications for FDA Policy*, 316 J. AM. MED. ASS'N 2357 (2016).

²⁰⁹ See Part II, *supra*. Many, although not all, of the approved and cleared non-therapeutic uses were also discovered through therapeutic uses—or at least developed after authorization of a therapeutic uses.

²¹⁰ See, e.g., New Statistics reveal the Shape of Plastic Surgery, <https://www.plasticsurgery.org/news/press-releases/new-statistics-reveal-the-shape-of-plastic-surgery> (reporting that roughly 17.5 million cosmetic procedures were performed in the United States in 2017).

²¹¹ See, e.g., Walker, *supra* note 138.

valuable information.²¹² The section explores how the FDA's past approach to regulating non-therapeutic uses aligns with the goals of its gatekeeping function. It demonstrates that the rationales for FDA gatekeeping permit flexibility in how the FDA implements its authority over non-therapeutic uses, and support the agency's chosen approach, at least for currently marketed technologies. If new non-therapeutic uses emerge—particularly outside the aesthetic context—there may be reason to revisit the FDA's approach.

Indeed, although consumer interest—and therefore strong industry interest—in non-therapeutic drug and device use is nothing new, non-therapeutic uses of drugs and devices may now be poised to become a bigger part of the FDA's regulatory portfolio for several reasons. One reason is that we are currently in a moment of intense interest in recreation and self-improvement through technological means, as evinced, for example, by the rise of various do-it-yourself (DIY) or citizen science movements, including “neurohackers” seeking to enhance cognitive performance, “lifehackers” using data collection technologies to track information about themselves to use in self-improvement, and “biohackers” carrying out self-experimentation with gene therapies and other synthetic biology techniques.²¹³

At the same time, there is hope that emerging technologies may prove to be safer or more effective for non-therapeutic uses than current technologies have been.²¹⁴ As one example, some believe that non-invasive, electro-

²¹² See, e.g., Eisenberg, *The Role of the FDA in Innovation Policy*, *supra* note 27; Kapczynski, *supra* note 27; Ariel Katz, Pharmaceutical Lemons: Innovation and Regulation in the Drug Industry, 14 MICH. TELECOMM. & TECH. L. REV. 1, 13 (2007); see also FDA MEMO, *supra* note 27 (offering numerous other justifications for the FDA's gatekeeping role, such as protecting subjects in clinical trials); cf. President John F. Kennedy, Special Message to the Congress on Protecting the Consumer Interest (Mar. 15, 1962), available at <http://www.presidency.ucsb.edu/ws/?pid=9108> (describing four consumer rights: the right to safety, the right to be informed, the right to choose, and the right to be heard).

²¹³ See, e.g., Anna Wexler, *The Social Context of 'Do-It-Yourself' Brain Stimulation: Neurohackers, Biohackers, and Lifehackers*, 11 *Frontiers in Human Neuroscience* 224 (2017).

²¹⁴ Many products that traditionally have been used for non-therapeutic purposes have been ineffective or unsafe. For example, there is limited evidence that ADHD drugs used off-label significantly improve cognitive performance and a dietary supplement company recently conducted a study comparing the cognitive enhancing effects of coffee with that of its own so-called “nootropic” supplement—and found that coffee worked better than its own product. See, e.g., Shaheen E. Kakhan and Annette Kirchgessner, *Prescription Stimulants in Individuals with and without Attention Deficit Hyperactivity Disorder*, 2 BRAIN AND BEHAVIOR 661, 666-69 (2012); Chrissy Farr, *This Start-Up Raised Millions to Sell 'Brain-Hacking' Pills, But its Own Study Found Coffee Works Better*, CNBC (Nov. 30, 2017), <https://www.cnbc.com/2017/11/30/hvmn-nootrobox-study-smart-pill-less-effective->

stimulation of the brain will prove to enhance athletic or cognitive performance, and more safely than cognitive or athletic performance enhancing drugs do.²¹⁵ Human genome editing provides a more dramatic example of an evolving technology with potential enhancement uses.²¹⁶ After decades of work to develop gene therapies, new techniques, such as CRISPR, have made genome editing easier and cheaper to carry out. And 2017 brought the first FDA approvals for gene therapies—for retinal disease that can lead to blindness,²¹⁷ acute lymphoblastic leukemia,²¹⁸ and non-Hodgkin lymphoma.²¹⁹ This technology, however, also might be used for non-therapeutic purposes. For example, a genetic intervention that effectively builds muscle might treat patients with muscular dystrophy *and* be used for healthy individuals interested in enhancing physical performance.²²⁰ But outside of rare examples, like building muscle tissue, where therapeutic and non-therapeutic purposes overlap, “the specificity of edited cells will make [off-label] applications less likely” than for traditional drugs and devices—making them more likely to undergo FDA review.²²¹

While technologies are evolving so, too, is law and policy, which may lead to more non-therapeutic uses coming before the FDA. For example, the 21st Century Cures Act of 2016 amended the FDCA to permit the FDA to consider “real world evidence” when evaluating new uses of already approved products.²²² Real world evidence includes “data regarding the usage, or the potential benefits or risks, of a drug derived from sources other

than-caffeine.html. New technologies also may simply offer new ways for consumers to use drugs and devices for non-therapeutic purposes. For example, there have been media reports of consumers using FitBits to monitor their heart rate while using illicit recreational drugs, such as cocaine. *See* Chrissy Farr, *People Are Using FitBits and Apple Watches to Monitor Their Heart Rate When Binging on Drugs—And Doctors Say It’s a Bad Idea*, CNBC (July 9, 2018), <https://www.cnbc.com/2018/07/09/apple-watch-and-cocaine.html>.

²¹⁵ *See, e.g.*, Bikson et al., *supra* note 185; Landhuis, *supra* note 190.

²¹⁶ *See, e.g.*, NATIONAL ACADEMIES OF SCIENCES, ENGINEERING & MEDICINE, HUMAN GENOME EDITING: SCIENCE, ETHICS, AND GOVERNANCE 137 (2017).

²¹⁷ Luxturna Labeling, <https://www.fda.gov/downloads/BiologicsBloodVaccines/CellularGeneTherapyProducts/ApprovedProducts/UCM589541.pdf>.

²¹⁸ Kymriah Labeling, <https://www.fda.gov/downloads/BiologicsBloodVaccines/CellularGeneTherapyProducts/ApprovedProducts/UCM573941.pdf>.

²¹⁹ Yescarta Labeling, <https://www.fda.gov/downloads/BiologicsBloodVaccines/CellularGeneTherapyProducts/ApprovedProducts/UCM581226.pdf>.

²²⁰ *See, e.g.*, HUMAN GENOME EDITING REPORT, *supra* note 216 at 9.

²²¹ *Id.* at 152.

²²² Pub. L. No. 114-255 § 3022, 130 Stat. 1033 (2016); *see also* Paradise, *21st Century Pharma*, *supra* note 207.

than randomized clinical trials,” such as from clinical practice.²²³ Depending on how the FDA implements this provision, it may allow manufacturers to seek authorization of non-therapeutic uses that are developed based on experience in clinical practice—such as the evidence showing that patients using the active ingredient in Rogaine for hypertension also experienced hair growth.²²⁴ If manufacturers are not required to conduct expensive clinical trials, they may be more likely to seek FDA authorization of non-therapeutic uses that do arise.²²⁵ Likewise, other legal and policy developments may encourage FDA involvement with non-therapeutic uses—such as the widespread state level decriminalization of cannabis that has allowed quasi-legal markets to emerge, which ultimately may lead the FDA to face questions about both medical and recreational cannabis products.²²⁶ These developments suggest that it is an opportune moment to consider how the purposes of FDA gatekeeping apply to non-therapeutic uses.

1. Consumer Protection

Traditionally, protecting consumers is identified as the rationale for requiring the FDA’s premarket authorization of drugs and devices.²²⁷ The FDA protects patients and consumers by helping to ensure that marketed drugs and devices have a favorable benefit-risk ratio for their intended uses.²²⁸ This view of FDA gatekeeping is consistent with the agency’s mission as described in the FDCA—ensuring that marketed drugs and

²²³ *Id.*

²²⁴ Jacqueline Corrigan-Curay et al., *Real-World Evidence and Real-World Data for Evaluating Drug Safety and Effectiveness*, JAMA (2018); Rachel E. Sherman et al., *Real World Evidence—What Is It and What Can It Tell Us?*, 375 NEJM 2293 (2016); Jonathan P. Jarow et al., *MultiDimensional Evidence Generation and FDA Regulatory Decision Making: Defining and Using “Real-World” Data*, 318 JAMA 703 (2017); U.S. FOOD & DRUG ADMIN., GUIDANCE: REAL-WORLD EVIDENCE TO SUPPORT REGULATORY DECISION-MAKING FOR MEDICAL DEVICES (2017); *see also* W. Nicholson Price II, *Drug Approval in a Learning Health System*, 102 MINN. L. REV. 2413 (2018) (“[I]f FDA learns more about drugs based on how they work in the real world, that information should be used to address how drugs are labeled, sold, and used.”).

²²⁵ On the other hand, if the FDA loosens its restrictions on off-label promotion—as a result of First Amendment jurisprudence or for other reasons—manufacturers may have fewer incentives to seek FDA authorization of non-therapeutic uses for already-approved drugs and devices. FDA MEMO, *supra* note 27; Kapczynski, *supra* note 27.

²²⁶ *Cf.* O’Connor & Lietzan, *supra* note 189.

²²⁷ *See, e.g.*, Eisenberg, *The Role of the FDA in Innovation Policy*, *supra* note 27; *see also* Epstein, *Against Permittitis*, *supra* note 17 at 3 (describing the “common justification” for FDA approval of drugs as “state intervention is necessary to guard against the exploitation of incompetent patients by unscrupulous purveyors of medical care.”).

²²⁸ *See, e.g.*, FDA MEMO, *supra* note 27.

devices are safe and effective and made available promptly.²²⁹ It is also consistent with the history of drug and device regulation in the United States.²³⁰ Many instances in which Congress has granted greater authority to the FDA have followed public health tragedies resulting from unsafe products, such as widespread birth defects associated with the use of thalidomide, a drug to treat morning sickness, in 42 countries.²³¹

But developing information to understand a drug or device's benefits and risks can take a long time. No reasonable premarket development program can provide complete certainty about a drug or device's risks and benefits, nor, realistically, can access to drugs and devices be delayed indefinitely until absolute certainty is reached.²³² Accordingly, the FDA must make its decisions to authorize drugs and devices in the context of some uncertainty.²³³

One way to conceptualize the FDA's task is that, in implantation of its premarket authorization processes, the FDA must balance the risk of making Type I errors—in which the agency authorizes an unsafe or ineffective drug or device—against the risk of making Type II errors—in which the agency fails to authorize a safe and effective drug or device.²³⁴ Making too many Type I errors will subject patients and consumers to harmful products and undermine public trust in the agency.²³⁵ Making too many Type II errors would deny patients access to often desperately needed therapies.²³⁶

In the context of therapeutic uses of products, scholars have debated whether the FDA is currently striking the right balance between these two kinds of errors, with some concluding that the FDA fails to sufficiently minimize Type I errors and others arguing the agency fails to sufficiently

²²⁹ 21 U.S.C. § 393.

²³⁰ See, e.g., Merrill, *supra* note 80 at 1704.

²³¹ See, e.g., Merrill, *supra* note 80 at 1764; Bara Fintel et al., *The Thalidomide Tragedy: Lessons for Drug Safety and Regulation*, HELIX (July 28, 2009), <https://helix.northwestern.edu/article/thalidomide-tragedy-lessons-drug-safety-and-regulation>.

²³² See, e.g., Zettler & Lietzan, *supra* note 32; cf. David E. Bernstein, *What to Do About Federal Agency Science: Some Doubts About Regulatory Daubert*, 22 GEO. MASON L. REV. 549, 562 (2015) (“An agency often has no choice but to rely on a certain amount of speculation based on limited data; indeed, agencies are often legally required to do so to fulfill their regulatory mandates. So long as an agency is doing the best it can with the available data, it is acting lawfully.”).

²³⁴ See Rachel E. Sachs, *Delinking Reimbursement*, 102 MINN. L. REV. 2307, 2323 (2018).

²³⁵ See, e.g., *id.*

²³⁶ See *id.*

minimize Type II errors.²³⁷ The appropriate balance also might change depending on the precise therapeutic context. A new drug for a terminal disease that lacks any currently available therapies may pose a very different question than a new blood pressure medication that is no more effective nor any safer than the numerous such medications already on the market. In fact, some advocacy groups and scholars have argued that patients in the former group have a protected liberty interest in accessing medical interventions, regardless of whether the FDA has authorized their use.²³⁸

The question of how to strike the balance between Type I and Type II errors in the context of non-therapeutic uses, however, might lend itself to a quite different analysis. Arguably, avoiding Type I errors is more important for non-therapeutic than therapeutic uses.²³⁹ Under this view, because the benefits of a non-therapeutic use are inherently less than those of a therapeutic use, the risks of a non-therapeutic use should be quite low, or the benefits quite high (or both), for the FDA to determine that the product's benefits outweigh them.²⁴⁰ That is, the FDA should err on the side of protecting consumers from risky and ineffective non-therapeutic uses, particularly where consumers do not have the same interest in access that terminally and seriously ill patients do. This might lead the FDA, for example, to refuse to approve Botox and dermal fillers for aesthetic uses, because of the risk of death associated with both.²⁴¹

Yet this approach is not the one that the FDA has implemented. The agency's approach, instead, might be consistent with a view that minimizing Type I errors is *less* important for non-therapeutic than for therapeutic uses.²⁴² For therapeutic uses, patients may not have much choice as to whether to use a particular drug or device a practical matter—there may be only one therapy for their disease or condition, or their choice may be dictated by their physician's views or prescribing decisions. Moreover, health insurers might not have much choice in deciding whether

²³⁷ See, e.g., Kemp & Prasad, *supra* note 16; Downing et al., *supra* note 16; Beckner, *supra* note 17; Epstein, *supra* note 17.

²³⁸ See, e.g., Abigail All. for Better Access to Developmental Drugs v. von Eschenbach, 495 F.3d 695 (D.C. Cir. 2007); see also Seema Shah & Patricia J. Zettler, *From A Constitutional Right to A Policy of Exceptions: Abigail Alliance and the Future of Access to Experimental Therapy*, 10 YALE J. HEALTH POL'Y, L. & ETHICS 135, 141 (2010); Patricia J. Zettler & Henry T. Greely, *The Strange Allure of State "Right to Try" Laws*, 174 JAMA INTERNAL MED. 1885 (2014).

²³⁹ See, e.g., Mehlman, *supra* note 10.

²⁴⁰ See, e.g., Lamkin, *supra* note 10; Mehlman, *supra* note 10.

²⁴¹ See Part II, *supra*.

²⁴² Cf. Zettler, *tDCS*, *supra* note 9 (raising this argument as a possibility).

or not to pay for therapeutic uses once approved by the FDA.²⁴³ Thus, under a view that minimizing Type I errors is less important for non-therapeutic uses, *patients* might merit a high level of protection from dangerous or ineffective therapies that, in essence, their disease or condition would force them to take (and that the health care system would be forced to pay for).²⁴⁴ *Consumers*, on the other hand, who voluntarily elect to engage in non-therapeutic uses, whether for enhancement or recreation, may be in need of less protection (assuming a free choice, including that the non-therapeutic products are not addictive).²⁴⁵ Indeed, we permit the marketing of all kinds of consumer products—including those that can cause grave harm when designed or manufactured incorrectly—to be marketed without a premarket review process.²⁴⁶ Similarly, perhaps we should permit consumers to choose whether to use Botox or dermal fillers, so long as they are informed of the relevant risks.

There also may be pragmatic reasons for the FDA to be less concerned about Type I errors for non-therapeutic uses than for therapeutic uses.²⁴⁷ For example, agencies might elect to regulate cautiously or not at all to “avoid backlash and to preserve their own political capital.”²⁴⁸ That is, rather than set a high bar for authorization of non-therapeutic uses, the FDA might not want to preserve political capital for fights over its decisions about controversial therapeutic uses, such as its controversial decision to withdraw approval of Avastin’s breast cancer indication.²⁴⁹

Likewise, there are arguments that minimizing Type II errors is either equally or less important in the non-therapeutic as compared to the therapeutic context. The belief that individuals have a right to choose which

²⁴³ See, e.g., Sachs, *supra* note 234.

²⁴⁴ As FDA Commissioner Scott Gottlieb recently said regarding copayments for chemotherapy drugs, “[i]s a patient really in a position to make an economically-based decision . . . Of course not.” U.S. Food & Drug Admin., Capturing the Benefits of Competition for Patients, <https://www.fda.gov/NewsEvents/Speeches/ucm599833.htm>.

²⁴⁵ It is worth noting that some of the social or ethical concerns about non-therapeutic uses, and in particular enhancing uses, involve the idea that consumers will not or do not freely choose enhancement, but instead opt to enhance their appearance or performance because of societal pressure to do so. See e.g., Fitz et al., *supra* note 10. But, whatever pressures there are to undertake enhancements (at least those currently available), that pressure is almost certainly not equivalent to the position a patient with terminal or serious condition with one or few therapeutic options finds himself or herself in.

²⁴⁶ For example, although infant toys are subject to numerous required specifications under the Consumer Product Safety Commission’s (CPSC) authority, they are not individually reviewed and approved by the CPSC. If improperly made, such toys can seriously injure, and even kill, children.

²⁴⁷ Jacobs, *supra* note 30.

²⁴⁸ *Id.* at 569.

²⁴⁹ See U.S. Food & Drug Admin., Avastin Information, <https://www.fda.gov/Drugs/DrugSafety/ucm193900.htm>.

therapeutic interventions to use without government interference is a long-standing, and strong, one in the United States.²⁵⁰ Such views might apply with even more force outside the therapeutic setting, where justifications for paternalistic regulatory approaches limiting personal choice may not be persuasive even to those who endorse them for products intended to address disease or maintain health.²⁵¹ These views may suggest that minimizing Type II errors is at least as important in the context of non-therapeutic products.

On the other hand, virtually all stakeholders agree that therapies for terminally and seriously ill patients should reach the market as quickly as possible.²⁵² The disagreement lies primarily in how much and what kinds of evidence are needed before such therapies are marketed (*i.e.*, in how to operationalize “as quickly as possible”).²⁵³ The same fundamental agreement is not likely to be found for non-therapeutic products. Although it is tragic to think of denying a group of terminally ill patients a safe and effective therapy, the same cannot be said of denying consumers a safe and effective recreational drug or cosmetic breast implants, for example. It may run counter to principles of individual autonomy, but it will not result in a consumer’s death, or in tangible harm to the consumer’s body. Nor would limiting access to non-therapeutic technologies as easily give rise to kinds of arguments rooted in individual’s liberty interests that terminally ill patients have put forth.²⁵⁴ Considering the possible concerns about Type I and Type II errors in the context of non-therapeutic uses, therefore, demonstrates that the FDA has considerable flexibility in how to implement its gatekeeping authority consistent with a consumer protection purpose.

²⁵⁰ Lewis A. Grossman, *The Origins of American Health Libertarianism*, 13 YALE J. HEALTH POL’Y, L. & ETHICS 76, 80 (2013); cf. Richard A. Epstein, *The Erosion of Individual Autonomy in Medical Decisionmaking: Of the FDA and IRBs*, 96 GEO. L.J. 559 (2008).

²⁵¹ Cf. Lawrence O. Gostin & K.G. Gostin, *A Broader Liberty: JS Mill, Paternalism and the Public’s Health*, 123 Public Health 214 (2009) (describing some paternalistic justifications for public health regulations).

²⁵² See, e.g., Shah & Zettler, *supra* note 238.

²⁵³ See, e.g., Kemp & Prasad, *supra* note 16; Downing et al., *supra* note 16; Beckner, *supra* note 17; Epstein, *supra* note 17.

²⁵⁴ Cf. Shah & Zettler, *supra* note 238. If enhancement becomes widespread such that it creates a “new normal,” problems of access may become more important. For example, if only wealthy individuals can access highly effective cognitive enhancers, that could reify or exacerbate societal inequalities. See e.g., Anita Allen and Nicolle Strand, *Cognitive Enhancement and Beyond: Recommendations from the Bioethics Commission*, 19 TRENDS IN COGNITIVE SCIENCE 549 (2015). Such access problems, however, typically are not about the initial question of FDA authorization based on safety and effectiveness—but on how technologies are distributed once demonstrated safe and effective.

2. Information Asymmetries

Related to the idea that the FDA's gatekeeping function protects consumers from unsafe and ineffective drugs and devices, is the view that the agency's premarket authorization processes address information asymmetries between consumers and manufacturers.²⁵⁵ Drugs and devices are described as "credence goods," meaning their safety, effectiveness, and quality cannot be readily and easily evaluated by consumers.²⁵⁶ For this reason, FDA gatekeeping is needed to "protect misinformed [or uninformed] consumers from better-informed sellers."²⁵⁷ As with consumer protection, this rationale for the FDA's premarket authorization power is paternalistic, but focuses on fixing this imbalance in information rather than protecting consumers from the products themselves.²⁵⁸

And similar to consumer protection, the FDA could reasonably take different approaches to regulate non-therapeutic uses consistent with the goal of correcting information asymmetries. On the one hand, information asymmetries may not be as pronounced for at least certain therapeutic uses. Consumers may be well-equipped to decide if aesthetic uses of drugs and devices are effective. Indeed, the FDA frequently has relied on patient-reported improvements as a primary indicator of such products' effectiveness, such as with hair growth drugs, Botox, Kybella, and dermal fillers.²⁵⁹ Recreational products—where the goal is to provide the consumer with some fun—likewise may be easily assessed by users themselves. If non-therapeutic uses of products are experience goods—that consumers can learn about through use—rather than credence goods, the FDA might

²⁵⁵ See, e.g., HENRY G. GRABOWSKI & JOHN M. VERNON, *THE REGULATION OF PHARMACEUTICALS* 7 (1983); Ariel Katz, *Pharmaceutical Lemons: Innovation and Regulation in the Drug Industry*, 14 MICH. TELECOMM. & TECH. L. REV. 1, 13 (2007); Kapczynski, *supra* note 27. Like the consumer protection rationale for FDA gatekeeping, the goal of addressing information asymmetries can be viewed as consistent with the long history of concern about unsupported safety and effectiveness claims about drugs and devices. For example, in 1907 the federal government sought to prohibit the sale of drugs sold as "effective in curing cancer, the defendant well knowing that such representations were false." Although the Supreme Court concluded that federal law at the time did not prohibit such "misleading statements," shortly thereafter Congress amended the law to do just that. Concerns about product sellers defrauding consumers are, at their core, concerns about information. *United States v. Johnson*, 221 U.S. 488, 495 (1911); Roseann B. Termini & Anthony Knabb diDonato, *The Role and Mission of the United States Food and Drug Administration: Regulator, Watchdog, Facilitator or "All of the Above,"* 7 BIOTECHNOLOGY & PHARMACEUTICAL L. REV. 1, 4 (2014).

²⁵⁶ Katz, *supra* note 255 at 13.

²⁵⁷ *Id.* at 8.

²⁵⁸ *Id.* at 8; Kapczynski, *supra* note 27.

²⁵⁹ See Part II, *supra*.

reasonably decide its premarket review need not be as stringent as for therapeutic uses.²⁶⁰

On the hand, not all non-therapeutic uses may be experience goods. Unlike aesthetic and recreational uses with benefits that consumers may be able to assess for themselves, consumers may have difficulty assessing the effectiveness of enhancing uses. As one example, Ritalin and Adderall, which are commonly used for academic performance enhancement and hyped as effective performance enhancers, have been shown to have only small effects on performance in studies, primarily in subjects that were lower-performing.²⁶¹ Although researchers have concluded that there is “limited support for the enthusiastic portrayal of cognitive enhancement” resulting from using these drugs, use remains widespread possibly because consumers cannot effectively evaluate the benefits of using the drugs for cognitive enhancement for themselves.²⁶² Moreover, the risks of non-therapeutic uses of drugs and devices are generally similar to those of therapeutic uses.²⁶³ Regardless of whether consumers can evaluate the benefits of a non-therapeutic use for themselves, consumers may not be able to easily predict and evaluate risks of non-therapeutic uses, just as patients cannot readily predict and evaluate the risks of therapeutic uses.²⁶⁴

3. Information Production

In addition to its other purposes, as Rebecca Eisenberg has explained, a third, and important, rationale for FDA gatekeeping is that it solves an informational production problem by requiring companies to produce rigorous evidence sufficient to assess the merits of their products.²⁶⁵ That is, we need the FDA’s premarket review processes because manufacturers are

²⁶⁰ Cf. Katz, *supra* note 255 at 13 (describing experience and credence goods).

²⁶¹ See, e.g., Shaheen E. Kakhan and Annette Kirchgeßner, *Prescription Stimulants in Individuals with and without Attention Deficity Hyperactivity Disorder*, 2 BRAIN & BEHAVIOR 661, 666-69 (2012).

²⁶² *Id.*

²⁶³ See Part XII, *supra*.

²⁶⁴ Cf. *Canterbury v. Spence*, 464 F.2d 772, 782 (D.C. Cir. 1972) (“To the physician, whose training enables a self-satisfying evaluation, the answer may seem clear . . . To enable the patient to chart his course understandably, some familiarity with the therapeutic alternatives and their hazards becomes essential”).

²⁶⁵ Eisenberg, *The Role of the FDA in Innovation Policy*, *supra* note 27; see also FDA MEMO, *supra* note 27; Kapczynski, *supra* note 27. This is not to suggest that the FDA’s information production role is unlinked to its consumer protection or information asymmetry roles. As Nathan Cortez and co-authors have explained, “[t]he true challenge, however, is creating a regulatory framework that encourages high-value innovation while also preventing the market from being overcome with products that are ineffective or unsafe.” Cortez et al, *supra* note 192 at 376.

otherwise not likely to produce the extensive, expensive information necessary to understand the effects of their products and the FDA has the expertise to assess the information.²⁶⁶ Retaining this incentive to produce information about the effects of drugs and devices is one reason that FDA policies generally prohibit manufacturers from promoting off-label uses—if permitted to promote those uses without FDA authorization, manufacturers would lack an incentive to study them first.²⁶⁷ Producing information about drugs and devices, in turn, helps to incentivize high value innovation—the creation of products for which there is reasonable certainty that products will do what their sellers claim.²⁶⁸ As Amy Kapczynski put it, “[w]e need the FDA to play this [gatekeeping] role because it is, quite simply, extraordinarily hard to know whether something is or is not a cure.”²⁶⁹

But in the non-therapeutic context—where we are *not* focused on cures—again the analysis might differ. It may be reasonable to be less concerned about information production for non-therapeutic uses. Outside of the context of medical therapies, we rarely require consumer product sellers to produce rigorous information about their products. We want to be sure that the data support claims that an intervention is a therapy and we prioritize incentivizing the creation of innovative and effective therapies, particularly for terminal and serious illness that lack satisfactory treatments. The same may not be true for non-therapeutic uses of drugs and devices. For example, it is, almost certainly, not a societal priority to incentivize the creation of innovative new wrinkle-eliminating drugs that improve on Botox. Indeed, this may be part of the reason that the FDCA carves out of the drug and device definitions—and the FDA’s gatekeeping function—a number of non-therapeutic uses.

In contrast, incentivizing information production may be just as important for non-therapeutic drugs and devices as for therapeutic ones, particularly if we consider non-therapeutic uses that are enhancing or recreational. There is tremendous hope about many non-therapeutic technologies. For example, a highly effective and safe cognitive enhancement technology could be revolutionary in what it allows individuals, and society at large, to accomplish.²⁷⁰ Likewise, to the extent that humans have long engaged in using substances for recreation and seem unlikely to abstain altogether anytime soon, a product with a safe, non-addictive, recreational use could provide a significant public health benefit. To realize that promise—or simply to ascertain whether that promise has

²⁶⁶ See, e.g., Kapczynski, *supra* note 27.

²⁶⁷ See, e.g., FDA MEMO, *supra* note 27; Kapczynski, *supra* note 27.

²⁶⁸ See, e.g., Katz, *supra* note 212.

²⁶⁹ Kapczynski, *supra* note 27 at 2358.

²⁷⁰ See, e.g., Allen & Strand, *supra* note 254.

been realized—it would be critical to have rigorous information about the risks and benefits of such technologies. High hopes for innovation in the enhancement or recreational space might lead to a conclusion that FDA gatekeeping is useful, and even necessary.²⁷¹

Moreover, although the FDA is not authorized to decide social and moral questions about non-therapeutic uses, rigorous information about the safety and effectiveness of non-therapeutic products might be necessary for individuals, or society, to answer those questions. For example, we might think differently about the widespread use of cognitive enhancement technologies with very low risks than we would about such technologies associated with high risks or a high level of uncertainty about their risks. Similarly, we might think differently about such technologies that effectively enhance cognitive capabilities in short term, than technologies that permanently change one's abilities. In short, the FDA reasonably could make very different choices with respect to how to apply its gatekeeping authority to non-therapeutic uses consistent with its information production role.

CONCLUSION

Although discussions about the FDA's drug and device premarket review authorities often focus on the agency's role in regulating important therapies, numerous non-therapeutic uses also are subject to FDA gatekeeping. Considering examples of how the agency has implemented this authority reveals that, at least for aesthetic uses, the agency has not treated non-therapeutic uses significantly differently than therapeutic uses. The agency is willing to authorize non-therapeutic uses even when they are associated with small benefits, serious risks, or both, and will accept various forms of effectiveness evidence for non-therapeutic uses including subjects' own evaluations of the effects. As with therapeutic uses, the agency also declines to enforce requirements for premarket review in some instances.

Such an approach, in which the agency concludes that arguably trivial non-therapeutic benefits can outweigh serious risks including death, may seem to contradict the public health mission of the agency. But the agency has considerable flexibility in implementing its gatekeeping authorities consistent with rationales for granting the FDA that power, and may be justified in treating consumers, who elect to use non-therapeutic uses, as in need of less protection than patients. However, if—as some

²⁷¹ Cf. Cortez et al, *supra* note 192.

hope—new non-therapeutic uses are developed for performance-enhancement or recreation, the agency’s approach may need to be re-evaluated.