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Drugs' Other Side Effects

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Drugs' Other Side-Effects

Craig J. Konnoth*

ABSTRACT: Drugs often induce unintended, adverse physiological reactions in those that take them—what we commonly refer to as “side-effects.” However, drugs can produce other, broader, unintended, even non-physiological harms. For example, some argue that taking Truvada, a drug that prevents HIV transmission, increases promiscuity and decreases condom use. Expensive Hepatitis C treatments threaten to bankrupt state Medicaid programs. BiDil, which purported to treat heart conditions for self-identified African-Americans, has been criticized for reifying racial categories. Although the Food & Drug Administration (“FDA”) has broad discretion under the Food, Drugs, and Cosmetics Act (“FDCA”) to regulate drugs, it generally considers only traditional side-effects. Neither the agency, courts, nor scholars have offered a systematic account of how to regulate collateral effects that do not involve direct physiological harm to the drug’s recipient.

This Article more clearly defines these harms and explains why and how the FDA should take them into account. It starts by offering three characteristics that distinguish these harms from those the FDA traditionally considers. First, unlike traditional harms, these harms are often the indirect rather than direct result of drug consumption. Second, they often affect third parties rather than the person that ingests the drug. Third, they might often raise non-health considerations, such as economic or moral concerns.

Both ethically and legally, the FDA should take into account such indirect, third-party, and non-health harms to some degree at least. Bioethical considerations, administrative accountability and practice, as well as pragmatic policy interests, all counsel considering these harms. But how should the FDA do so? As the Article explains, the FDCA offers a variety of choices for FDA intervention, ranging in intensity from flat approval refusals to mandating labeling or prescription guidelines. In most cases, various considerations suggest that more limited forms of intervention are usually appropriate to address these harms.

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I.	INTRODUCTION.....	173
II.	DESCRIBING THE PROBLEM.....	178
	A. <i>THE FDA OVERSIGHT PROCESS</i>	178
	B. <i>CABINING THE QUESTION</i>	181
III.	DRUG WARS.....	183
	A. <i>INDIRECT HARMS</i>	183
	B. <i>THIRD-PARTY EFFECTS</i>	186
	C. <i>NON-HEALTH EFFECTS</i>	189
	D. <i>SHORTCOMINGS</i>	193
	1. Lack of Collection of Data or Assessment of Concerns.....	193
	2. Failure of Process to Incorporate Data into Concerns.....	195
	3. Lack of Systematization Across Drugs.....	195
IV.	THE ETHICAL CASE FOR CONSIDERING ‘OTHER’ SIDE-EFFECTS ...	196
	A. <i>INDIRECT HARMS</i>	196
	B. <i>THIRD-PARTY EFFECTS</i>	199
	C. <i>NON-HEALTH EFFECTS</i>	202
V.	THE POLICY CASE FOR CONSIDERING ‘OTHER’ SIDE-EFFECTS.....	207
	A. <i>CONSEQUENTIALISM</i>	207
	B. <i>ACCOUNTABILITY AND LEGITIMACY</i>	211
	C. <i>INFORMATION</i>	215
	D. <i>OBJECTIONS</i>	216
	1. Time and Cost.....	216
	2. The Kitchen Sink/Overreach Objection.....	218
	3. Expertise.....	219
	4. Federalism.....	221
VI.	REGULATORY CALIBRATION.....	223
	A. <i>DESCRIBING REGULATORY CALIBRATION</i>	223
	B. <i>JUSTIFYING CALIBRATION</i>	226
	C. <i>STATUTORY CALIBRATION</i>	230
	1. Approval.....	231
	2. Advertising/Labeling Review.....	233
	3. Post Approval/Marketing Power.....	234
	4. Adjusting the Process.....	234
VII.	CONCLUSION.....	235

I. INTRODUCTION

Drugs produce side-effects—that is, unintended, incidental, consequences of ingesting the drug.¹ Benadryl causes drowsiness;² Zolofl causes nausea;³ Warfarin might result in internal bleeding.⁴ Sometimes such side-effects are serious enough for the Food & Drug Administration (“FDA”) to deny approval of the drug.⁵ And the public hears of the side-effects of some drugs only after they are approved, marketed, and even prescribed.

Sometimes these side-effects are positive. NyQuil is frequently used as a sleep medication because it produces drowsiness.⁶ Manufacturers might even market these desirable side-effects.⁷ But most of the time, side-effects are negative, causing discomfort, danger, and even death. These side-effects have in common one important feature: they all involve physiological reactions to the chemical effects of the drug. Government agencies have been equipped to deal with these physiological effects—their experts can identify side-effects through the pre-approval clinical trials and post-approval drug surveillance, and their legal powers permit them to withhold or withdraw approval of drugs that have dangerous effects.⁸

1. Many of my concerns apply to food and devices as well. However, the cultural role that food plays renders distinguishing between main and side-effects impossible. The regulation of devices differs slightly from that of drugs—enough that clarity counsels focusing only on drugs for the purpose of this Article.

2. *Diphenhydramine Hydrochloride-Drug Summary*, PDR, <https://www.pdr.net/drug-summary/Diphenhydramine-Hydrochloride-diphenhydramine-hydrochloride-1140.941> [<https://perma.cc/H36P-FKQ4>]. Benadryl is a brand name of diphenhydramine hydrochloride.

3. *Sertraline Hydrochloride-Drug Summary*, PDR, <http://www.pdr.net/drug-summary/Zolofl-sertraline-hydrochloride-474.3608> [<https://perma.cc/HA6S-8FHS>]. Zolofl is the brand name of sertraline hydrochloride.

4. Charles Ornstein, *Popular Blood Thinner Causing Deaths, Injuries at Nursing Homes*, PROPUBLICA (July 12, 2015, 7:00 PM), <https://www.propublica.org/article/popular-blood-thinner-causing-deaths-injuries-at-nursing-homes> [<https://perma.cc/3KKJ-HBUX>] (“Coumadin (or warfarin) is a medicine often prescribed to older adults for prevention of strokes, blood clots and heart attacks. However, the dose must be closely monitored. Too much can lead to internal bleeding.”).

5. See W. Kip Viscusi & Richard J. Zeckhauser, *Regulating Ambiguous Risks: The Less than Rational Regulation of Pharmaceuticals*, 44 J. LEGAL STUD. 3387, 3388–89 (2015).

6. Christine Skopec, *The Most Dangerous Over-the-Counter Cold Medications*, SHOWBIZ CHEATSHEET (Dec. 5, 2017), <https://www.cheatsheet.com/health-fitness/dangerous-over-the-counter-cold-medications.html> [<https://perma.cc/MDR6-GHJN>]; David Warren, *Does Nyquil Help You Sleep? What You Need to Know [Experts Say]*, WFM HEALTH, <https://wealthformyhealth.com/does-nyquil-help-you-sleep> [<https://perma.cc/J7Q9-D68X>]. Though it is often marketed as such.

7. *United States Calming and Sleeping Market: New Insights*, COMPANIES & MKTS. (June 9, 2015, 10:12 PM), <https://advance.lexis.com/document/index?crd=23a32442-d5c1-42d0-a59a-bbfb5ebfbob&pdpermalink=co43930e-1f86-45bb-94c1-e678af38d170&pdmfid=1000516&pdisurlapi=true>. It is notable that off-label marketing is impermissible in FDA’s view. While labels indicate adverse effects, indicating that those are benefits might be construed as misleading in the FDA’s view.

8. See *infra* Part V.

But drugs can produce other kinds of effects that go far beyond chemical and physiological reactions. The birth control pill gave women autonomy that they never had before.⁹ More recently, pre-exposure prophylaxis (“PrEP”) has proven to prevent HIV transmission. This allows individuals to engage in intercourse without the fear of contracting HIV and may reduce the stigma that HIV positive individuals have suffered.¹⁰

Some may argue that these are, in fact, the main purpose of drugs. The point of wellness isn’t to have a body that functions optimally. Rather, its good lies in the other goals wellness allows us to pursue: autonomy, human connection, and happiness. Drugs are marketed with the promise of joy and productivity, rather than for producing health for its own sake.

But putting that issue to one side, my central point is that the introduction of drugs onto the market can have additional non-physical negative effects that are, most decidedly, unintended. Some argue that PrEP has led to increased promiscuity and a decline in condom usage.¹¹ The introduction of high cost drugs in the Hepatitis C context has siphoned resources away from other areas. Another drug, BiDil, which was famously understood to target heart conditions specifically for African-Americans was criticized for reifying racial categories.¹² These non-physiological effects can range from unintended changes in the behavior of individuals to broader effects on third parties or society as a whole.

However, the literature has a gap, in that it fails to abstract and analyze these problems—and the FDA’s engagement (or non-engagement) with them—more generally. At base, my claim is, that as a systematic matter the FDA regulates only (1) direct effects of the drug (2) on the person who takes it (3) because of its physiological effects. The harms that are not considered systematically are therefore (1) indirect effects, such as risk compensation behavior, or (2) effects on third parties or society, that is, those who have not taken the drug, or (3) effects that are non-physiological in nature, such as racial effects.¹³ This Article concedes that the FDA should continue to focus

9. For the classic 1971 grassroots account, see JUDY NORSIGIAN, *OUR BODIES, OURSELVES* 91 (2011) (“Our ability to prevent or delay pregnancy is fundamental to our ability to choose how we live our lives.”).

10. WORLD HEALTH ORG., *GUIDELINE ON WHEN TO START ANTIRETROVIRAL THERAPY AND ON PRE-EXPOSURE PROPHYLAXIS FOR HIV* 17, 29, 35 (Sept. 2015), https://apps.who.int/iris/bitstream/handle/10665/186275/9789241509565_eng.pdf?jsessionid=B2F46184E8EC35B7B512068B828D6BAE?sequence=1 [<https://perma.cc/S99L-FQ4K>]; Dawn K. Smith et al., *Attitudes and Program Preferences of African-American Urban Young Adults About Pre-exposure Prophylaxis (PrEP)*, 24 *AIDS EDUC. & PREVENTION* 408, 418–19 (2012).

11. Travis Gasper, *A Religious Right to Discriminate: Hobby Lobby and “Religious Freedom” as a Threat to the LGBT Community*, 3 *TEX. A&M L. REV.* 395, 413 (2015).

12. Michael Laufert, *Race and Population-Based Medicine: Drug Development and Distributive Justice*, 21 *GEO. J. LEGAL ETHICS* 859, 873, 876 (2008).

13. Though OIRA tracks the overall cost of FDA regulations, including drug approvals, neither OIRA nor the FDA consider the cost of the drugs being approved as a factor in cost-benefit analysis in the approval process. For an example of OIRA’s consideration of cost of new

primarily on direct, physiological, and first person side-effects, and might save its most onerous regulation for those contexts. However, I also claim that the FDA should take into account these “other” side-effects more systematically, and engage in *some* consideration and possible regulation, usually less onerous, based on them.

This is not to say that these effects are never, or even rarely, considered. In many cases, as I describe below, the FDA will take some of these harms into account. But the FDA does not explain why it does not consider these effects in some contexts and not others, or with respect to some drugs or not others. Indeed, in many cases, it appears that political pressure or one-off congressional action might produce the FDA review in this area.

The limited FDA literature on these matters has not helped address the FDA's ad hoc approach(es). Some scholars, to be sure, have addressed particular concerns that they believe that the FDA should take into account. To take a few prominent examples: Numerous scholars have argued that the FDA should take ethical concerns into account when approving drugs that result in human enhancement, such as human growth hormone.¹⁴ Scholars have recently argued that the FDA should take public health concerns into account, especially in the opioid context.¹⁵ Yet others have argued that the FDA should take into account the behavioral changes that PrEP and other drugs produced.¹⁶ And—to offer a counterexample—a court criticized the FDA for inappropriately taking into account political (some would call them ethical) considerations in delaying the approval of oral contraceptives.¹⁷

But, while each line of scholarship raises important considerations that I raise in this Article as appropriate, they do little to address the haphazard approach. They leave most of the harms I discuss above unaddressed. They also fail to systematize and taxonomize the harms, provide explanations for *when* the FDA should regulate them, and to what degree. They focus, rather, on powerfully elaborating the nature, degree, and extent of danger their particular harm—growth hormones, risk compensation, and the like—poses,

regulations, the office provides a database of the cost of all new regulations. *Information Collection Review Data, OFFICE INFO. & REGULATORY AFFAIRS*, <https://www.reginfo.gov/public/do/PRAMain;jsessionid=B2E7F59DCB150A06FA30CF988269E9D8> [<https://perma.cc/JP3G-B2L2>].

14. See, e.g., Dov Fox, *Safety, Efficacy, and Authenticity: The Gap Between Ethics and Law in FDA Decisionmaking*, 2005 MICH. ST. L. REV. 1135, 1184; see *infra* notes 145–49 and accompanying text.

15. Patricia J. Zettler et al., *Implementing a Public Health Perspective in FDA Drug Regulation*, 73 FOOD & DRUG L.J. 221, 225 (2018). Zettler et al. focus on opioid regulation. However, opioid regulation falls close enough to the core of the FDA's traditional approach that I do not rely on it heavily. Opioid addiction does not involve third parties, nor does it involve non-health effects. It might arguably involve indirect effects (to the extent that addiction is not a “direct” effect of usage) but that, too, is unclear. The opioid crisis therefore does not figure prominently in my analysis.

16. These battles most recently cover the approval of HIV prophylactic medication, which I examine in detail. See *infra* Section III.A.

17. This involved a series of decisions under both the Bush and Obama administrations. I discuss those decisions in greater detail in Section V.B.

to argue that the FDA take that particular harm into account. They also sometimes examine the precise statutory and regulatory provisions, such as public health provisions, that allow their particular harm to be incorporated within FDA analysis.

This Article fills this gap from both the bioethical and legal perspective. It taxonomizes the harms into broader categories, provides a theoretical analysis for FDA consideration of the harms in each category. Such an approach means that this Article incorporates a broader range of concerns and harms, most of which the legal literature has not examined. I explain that ethical and legal considerations taken together counsel the consideration of “other side-effects.” At the same time, it argues that its involvement should be calibrated depending on the harm in question. I explain how the broader statutory and regulatory logic permits, even mandates, such calibration.

Part II provides an overview of the FDA oversight process and explains why the problem I am trying to address differs from that which occupies traditional FDA scholarship. Next, Part III provides examples of each of these harms with minimal definition. It also shows that in some cases, the FDA does regulate these other party effects in certain ways, but also that there is little explanation for the method and kind of regulation the FDA has adopted in those areas. It is unclear whether the FDA should be doing more than it is doing, or less, whether it is addressing the right kinds of harms, without further examination.

The subsequent parts go about systematizing these other side-effects, arguing for regulation in some cases, and in others, justifying the nature of the regulation the FDA has engaged in so far. Part IV elaborates on the conceptual categories I draw—indirect, third-party, and non-health effects—and considers their ethical ramifications individually. Because ethical considerations undergird legal policy in both research and clinical practice, I also examine whether they permit consideration of other side-effects. I conclude that they do so, and indeed, in some cases, may mandate, such consideration.

Part V turns to legal, administrative, and policy considerations. Relying on administrative law scholarship in other areas, Part V argues that the essential logic of cost-benefit analysis (“CBA”) which should undergird much (albeit maybe not all) of the FDA’s analysis would require the FDA to take into account ancillary indirect, or third-party, or non-health effects (collectively, “other effects”). Further, values promoting information collection for decisionmaking, transparency and democratic accountability also require an explicit accounting of such considerations. Addressing objections, I note that such an approach would likely *save* time and money in the long run, is both analytically and practically feasible, and presents no constitutional difficulties.

Part VI argues that because the harms themselves exist on a spectrum, FDA action should be calibrated on a spectrum as well. Administrative law

scholarship has, for decades now, offered the vision of a so-called “enforcement pyramid,” where administrative actions range from lenient to more stringent.¹⁸ FDA action can similarly range from severe to mild, affecting manufacturers, providers, patients, and others. Scholars contemplate that the pyramid is useful from a game theory perspective; administrators can efficiently escalate penalties depending on the responsiveness of the regulated firm.¹⁹

However, such regulatory calibration can also track agency expertise and legitimacy. As in other areas of law, including constitutional law, common sense intuitions and existing statutory structure suggest that the action’s severity should range based on the certainty of the harm and the importance of the regulation’s purpose. I argue that indirect harms, third-party effects, and non-health effects are less certain and less within the FDA’s area of expertise and legitimacy than other harms. But rather than ignore those harms altogether, the FDA should, consistent with the statutory logic, generally exert some limited intervention to prevent those effects. The limited steps the FDA has adopted conforms to this statutory logic but should be further expanded.

A final caveat. The FDA regulates a range of products. This Article addresses only drugs. First, FDA regulation of drugs and devices have similarities. Yet, the relative novelty of device regulation by the FDA suggests a far more complex ontological and epistemological analysis than does that of drugs.²⁰ But much of what I say regarding FDA regulation of drugs applies to devices. Second, the FDA also regulates food, cosmetics, and dietary supplements among other items. But these items play a far more complex cultural role than do drugs, as a general matter. FDA’s regulation of food is less pervasive; it refrains, as it should, from intervening in the mostly non-technical processes that construct the meaning of those items in our lives. Finally, animal drugs and tobacco, also FDA regulated items are far more limited in scope and interest. Drugs, however, are a different story. The FDA is deeply involved in producing the roles that drugs play, albeit in conversation with other social discourses.

In many cases these ‘other’ side-effects can affect the drug approval process *sub silentio*. In some cases, social value debates around drugs may affect conversations about health delivery mechanisms unrelated to drug approval itself. Creating a forum to raise these values as part of the approval process

18. See generally IAN AYRES & JOHN BRAITHWAITE, *RESPONSIVE REGULATION: TRANSCENDING THE DEREGULATION DEBATE* (1992) (establishing the theory which has since been relied on heavily in administrative law scholarship).

19. See *id.*

20. This is not to deny the relative novelty of many drug technologies. DIY gene hacking, stem cell therapies, CRISPR, mtDNA transfer. See, e.g., Payam A. Gammage et al., *Mitochondrial Genome Engineering: The Revolution May Not Be CRISPR-ized*, 34 *TRENDS IN GENETICS* 101, 106–08 (2018).

might allow regulators and the public to openly engage with and understand these issues earlier on in the process.

Examining the ripple effects of drugs beyond the physiological realm demonstrates how health itself is discursively constructed. Accounting for these effects demonstrates the complex way in which broader community norms interact with and shape our understanding of health, and how health discourses exert their own pressure in return. Embedded within these discourses are claims about the relative value of different kinds of well-being, about the relative importance of individual versus community health, and the value of health more generally. The changes I prescribe will therefore invite continuous revision and reconstruction, which requires stripping scientific experts of exclusive jurisdiction, and bringing in society as a whole.

II. DESCRIBING THE PROBLEM

A. *THE FDA OVERSIGHT PROCESS*

To understand the problem I seek to unravel, it helps first to offer an overview of the FDA oversight process. One way to separate federal oversight of drug safety is in two periods. First, the FDA must approve the drug, along with labeling, and advertising. As part of this, it might also require a risk mitigation strategy. Second, after the approval, the FDA engages in post-market surveillance, and might require further changes, or in the most extreme situations, withdrawal of the drug. At all times, the FDA has focused on maintaining the physical safety of those ingesting the drug.

In 1906, the six-page Pure Food & Drug Act prohibited manufacture and interstate transportation of “adulterated” and “misbranded” foods and drugs;²¹ 1912 amendments required the government to prove that the adulterer had engaged in fraudulent behavior. In 1938, Congress passed the Federal Food, Drug and Cosmetic Act (“FDCA”).²² The “most substantial innovation” of this Act was its approval regime—“manufacturer[s had] to submit a new drug application” (“NDA”) which had to include studies and labeling specimens.²³ The FDA could reject an application, though if it failed to act within 60 days, the application was considered approved.²⁴ In 1962, Congress

shifted the burden of proof from the FDA to the manufacturer. Before 1962, the agency had to prove harm to keep a drug out of the market, but the amendments required the manufacturer to demonstrate that its drug was “safe for use under

21. Federal Food and Drug Act of 1906, Pub. L. No. 59-384, 34 Stat. 768.

22. Federal Food, Drug, and Cosmetic Act of 1938, Pub. L. No. 75-717, 52 Stat. 1040 (codified as amended at 21 U.S.C. §§ 301-399i (2012)).

23. *Wyeth v. Levine*, 555 U.S. 555, 566 (2009).

24. 21 U.S.C. § 505(c).

the conditions prescribed, recommended, or suggested in the proposed labeling” before it could distribute the drug.²⁵

That regime remains in place today.

The approval process focuses on ensuring that the drug is physiologically safe and effective for ingestion. First, a manufacturer tests the drugs on animals. If animal testing proves promising, the manufacturer would submit an Investigational New Drug Application (“IND”), the approval of which allows it to test the drugs on humans in a three-phase process. At Phase I, a small group of individuals ingest the drug, to determine safe dosage ranges and side-effects. At Phase II, a larger group takes the drug to determine effectiveness, as well as to continue to investigate safety. At Phase III, yet a larger group takes the drug to determine effectiveness and to continue to develop knowledge about side-effects. Only once Phase III is complete might the sponsor file an NDA to market the drug. Thus, all stages of the approval process are geared towards experiments that focus on the effects of the drug on those taking it.

While FDA approval is one of the agency’s most important activities, it also has other powers. Three examples I will focus on in this overview are advertising and labeling, and the Risk Evaluation and Mitigation Strategy (“REMS”) program both of which occur pre-approval,²⁶ and post-market surveillance. However, each of these activities are related—for example, labeling might be part of a risk management strategy, and post market surveillance might lead to a change in labeling or REMS.²⁷

The 1906 Act gave the FDA limited power over labeling.²⁸ With approval powers in 1962, the act required the FDA to consider approval in light of the proposed labeling. Also, in 1962 it received power to regulate prescription drug advertising relating to safety and efficacy, transferring this power from the Federal Trade Commission. As it stands now, the FDA has the power to penalize “false or misleading” advertising.²⁹ It may also require information regarding “side effects, contraindications, and effectiveness” to be included in advertising or labeling. It is fair to assume that such information concerns narrower side-effects such as physiological or chemical reactions rather than broader side-effects. In addition to this, the FDA has the authority to prereview television advertisements in certain narrow circumstances.

As the FDA’s power has evolved, the focus of whom, is directly protected has also changed—but has remained ultimately, on individuals ingesting the

25. Drug Efficacy Amendment Act of 1962, Pub. L. No. 87-781, §§ 102(c), 104(b), 76 Stat. 780, 781, 784.

26. 21 U.S.C. § 355-1(a)(1).

27. *Id.* § 355-1(a)(2)(A).

28. *United States v. Johnson*, 221 U.S. 488, 496–97 (1911) (noting that the agency’s power was limited to false claims about drug ingredients).

29. 21 U.S.C. § 333(g).

drug or those providing the drug to them for ingestion. Thus, the Senate Report from the 1962 Amendments was primarily concerned with *physicians* prescribing the drug being “regularly inundated with a great mass of advertising and promotional material, much of which is misleading and some actually false.”³⁰ Similarly, the FDA justifies its oversight of such advertising “because *patients* are not able to use the drug safely on their own.”³¹ Further, its decisions about labeling and advertising are tied to the data that comes from the approval process.³² The FDA’s focus has therefore been on advertising and labeling issues as applied to the individual who ingests the drug.

Another key tool in the FDA arsenal consists of REMS programs that the agency might impose on drugs that it believes merit such measures. Those programs are integrated approaches that seek to reduce the adverse effects of the drugs. The concept is not new—many companies would voluntarily comply with risk mitigation strategies. But the 2007 FDA Amendments Act gave the FDA specific authority to require REMS.³³ The strategy might involve certain labeling and package inserts; however, it might also involve other measures. Notably, the measures again, focus on the person ingesting the drug. Three of the six (non-exhaustive) suggestions focus on the health settings or providers who dispense the drug, and who only, presumably, interact with the patient at the point of contact.³⁴ The other three focus on the wellbeing and monitoring of the patient. As described below, some REMS might take into account broader effects, but those approaches are not consistently enforced.

Finally, the 1962 Drug Amendments also required mandatory Adverse Drug Experience (“ADE”) reporting by manufacturers. The statute did not

30. S. Rep. No. 87-1744, at 1 (1962), as reprinted in 1962 U.S.C.A.N. 2884, 2898.

31. *Basics of Drug Ads*, FDA, <https://www.fda.gov/Drugs/ResourcesForYou/Consumers/PrescriptionDrugAdvertising/ucmo72077.htm> [<https://perma.cc/NJX8-B7DX>].

32. See, e.g., 21 U.S.C. § 355 (“[D]rug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof. . . .”). Seeking a change in labeling requires submitting a Supplemental New Drug Application, which has labeling related change codes. See *FDA Drug Approvals List*, FDA, <https://web.archive.org/web/20060102003757/http://www.fda.gov/cder/da/da.htm>. See generally Katherine A. Helm, Note, *Protecting Public Health from Outside the Physician’s Office: A Century of FDA Regulation from Drug Safety Labeling to Off-Label Drug Promotion*, 18 FORDHAM INTELL. PROP. MEDIA & ENT. L.J. 117, 152 (2007). Advertising similarly focuses on safety issues on those ingesting the drug. Wayne L. Pines, *A History and Perspective on Direct-to-Consumer Promotion*, 54 FOOD & DRUG L.J. 489, 500 (1999).

33. Barbara J. Evans, *Seven Pillars of a New Evidentiary Paradigm: The Food, Drug, and Cosmetic Act Enters the Genomic Era*, 85 NOTRE DAME L. REV. 419, 511–12 (2010).

34. The six “elements to assure safe use” (“ETASUs”) include the possibility that the “providers . . . have particular training or experience” that those dispensing the drug “are specially certified,” and that “the drug be dispensed to patients only in certain health care settings, such as hospitals.” 21 U.S.C. § 355-1(f)(3)(A)–(C). Conversely, the FDA might require the patients to provide evidence of “safe-use conditions, such as laboratory test results;” and that the patient be “subject to certain monitoring” or “registr[ation].” *Id.* § 355-1(f)(3)(D)–(F).

provide exact detail on what the experience would be, but did provide an approach for determining how to assess physiological risk on those ingesting the drug.³⁵ The 2007 FDA Amendments Act enhanced post-marketing surveillance, by, for example, allowing the FDA to mandate post-market clinical (Phase IV) trials. This focus on clinical trials again emphasizes the effects on individuals who take the medication.

While the statutory regime emphasizes a focus on the direct physiological effects on individuals who take the drug, there are also a lot of other effects that could be considered. In the next Sections, I explain what these effects are, and make the administrative and ethical case for considering them. Finally, I explain how the statute would accommodate taking into account these effects.

B. CABINING THE QUESTION

The question this Article raises is fundamentally one of FDA jurisdiction—what kind of problems can the FDA seek to solve. This should be distinguished from another jurisdictional question—namely what kind of items can the FDA regulate.

This latter question is the main preoccupation of much of FDA case law, which is why I emphasize its separate orbit. The statute gives the FDA the authority to regulate only a drug, food, cosmetic or medical devices.³⁶ The first FDA related cases to arrive in the federal courts for example, were concerned whether a particular item constituted a drug.³⁷ Courts would often look to labels as the source of the defendant's intent; such intent, in turn, dispositively classified the drug.³⁸

35. *Id.* § 355(k)(1); 21 C.F.R. § 314.80(a) (2016) (listing last minute edits).

36. Drugs are defined as substances listed in official compendia or “articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease . . . and . . . articles (other than food) intended to affect the structure or any function of the body” 21 U.S.C. § 321(g)(1). A device is an item with the same property but “which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes.” *Id.* § 321(h).

37. The Second Circuit Court of Appeals held that gauze bandages are a “drug” within the definition of the Pure Food and Drugs Act. *United States v. 48 Dozen Packages, More or Less, of Guaze Bandage Labeled in Part Sterilized*, 94 F.2d 641, 642 (2d Cir. 1938). In determining whether something should be considered a “drug,” early courts would analyze the intent of the distributor. The Fifth Circuit held that mineral water was considered a “drug” when the label included a list of diseases that the water would cure, including diabetes. *Bradley v. United States*, 264 F. 79, 82 (5th Cir. 1920).

38. In *U.S. v. Eleven Cartons of Drugs, etc.*, for example, the court held that an inhalant shipped through interstate commerce was a drug that had been misbranded because they did not indicate the quantity of alcohol the inhalant contained. *See United States v. Eleven Cartons of Drugs Labeled in Part ‘Vapex,’* 59 F.2d 446, 447–48 (1932). Similarly, a cure all mixture was considered a “drug,” when its packaging included a notice “that it has and will cure Tuberculosis.” *See Seven Cases (More or Less), Each Containing Twelve Bottles of Eckman’s Alternative, Eckman Mfg. Co. v. United States*, 239 U.S. 510, 514 (1916). For a more recent treatment, see generally

Although there is no doctrinal relevance, to understand the distinction between the two jurisdictional questions, analogous problems implicated by the jurisdiction of other entities—namely, courts—might prove illuminating. In determining jurisdiction, courts consider *inter alia*, two questions. (1) What kind of problem is before them, that is, what subject area it implicates. Article III courts address concrete, adverse, and particular questions related to federal law.³⁹ Tax and bankruptcy problems will go to other kinds of tribunals.⁴⁰ (2) Next, courts consider what entity or thing is causing the problem. Most must consider, at the very least whether there is in rem or in personam jurisdiction, or diversity among parties.⁴¹ Others may be limited in their reach to Indian tribes,⁴² juveniles,⁴³ or military personnel.⁴⁴

My claim here is that FDA case law has addressed the latter problem—what entities (food, drugs, etc.) that is causing the problem. But FDA law and policy have not reached what is arguably the more important question—what *kinds* of problems may the agency address.

The *assumption*, however, appears to be that regulation—both *ex ante* via the FDA, and *ex post* via the FDA and the tort regime—primarily should reach (1) physiological harms (2) that can be causally directly (or at least, physiologically) connected to the drug, which (3) affect the patient taking the

Patricia J. Zettler et al., *Closing the Regulatory Gap for Synthetic Nicotine*, 59 B.C. L. REV. 1933 (2018) (describing a more recent treatment).

39. See generally Craig Konnoth & Seth Kreimer, *Spelling Out Spokeo*, 165 U. PA. L. REV. ONLINE 47 (2016) (providing a framework for understanding Article III standing after Justice Alito's majority opinion in *Spokeo, Inc. v. Robins*, 136 S. Ct. 1540 (2016), in which the Justice distinguished between concrete and particularized injuries).

40. See 9 AM. JUR. 2D *Bankruptcy* § 717, Westlaw (database updated August 2019) (describing the bankruptcy jurisdiction). Other examples abound. Federal courts

are empowered to hear only those cases that (1) are within the judicial power of the United States, as defined in the Constitution, and (2) that have been entrusted to them by a jurisdictional grant by Congress. A federal court's entertaining a case that is not within its subject matter jurisdiction is no mere technical violation; it is nothing less than an unconstitutional usurpation of state judicial power. Accordingly, there is a presumption that a federal court lacks subject matter jurisdiction, [and the burden to show that it exists is on the party seeking to invoke federal jurisdiction].

13 FED. PRAC. & PROC. JURIS. *Courts of Limited Jurisdiction* § 3522 (3d ed. 2019); see also U.S. CONST. art. III, § 2.

41. For example, state long-arm statutes provide the statutory basis for jurisdiction, and Fed. R. Civ. Proc. 4(k) describes how to establish personal jurisdiction at the federal level. *International Shoe Co. v. Washington*, sets out limits on personal jurisdiction, requiring "minimum contacts" with the forum. See *Int'l Shoe Co. v. Washington*, 326 U.S. 310, 316 (1945). Jurisdiction may also turn on the status or classification of the person being regulated. Courts will assume jurisdiction when they can reach a certain individual because of their status. See 18 U.S.C. § 5032 (2012) (establishing juvenile courts).

42. See 18 U.S.C. § 1152 (establishing tribal courts).

43. See 57 C.J.S. *Military Justice* § 20 (2012) (establishing military courts).

44. See, e.g., *Munaf v. Geren*, 553 U.S. 674, 680, 685–89 (2008) (finding that the habeas corpus jurisdiction of federal courts extended to American citizens held in Iraq by a multinational force but under the control of American military officials).

drug. Similar criteria and distinctions appear in other jurisdictional contexts.⁴⁵ In what follows, I provide examples where at least one or more of these three conditions do not hold and the FDA still regulates, or fails to regulate, the problem, with no explanation as to its variable approach. Notably, however, many of these other side-effects have not been studied properly, which limits the documented examples I can provide.

III. DRUG WARS

A. INDIRECT HARMS

Although the FDA generally regulates harms that affect an individual directly, drugs might also harm individuals indirectly. These effects aren't caused by the chemical effect of the drug on physiology, but rather because an intervening cause—the patient, for example—chooses to engage in a particular behavior.

Examples abound. The first example of indirect harm occurs when the drug is designed to assist a certain activity, which itself poses certain risks. In the sexual context, Viagra is a useful example.⁴⁶ Viagra has been linked to an increase in sexually transmitted diseases (though causal effects have yet to be clarified).⁴⁷ Thus, some call “for greater responsibility in prescribing [erectile dysfunction] medications.”⁴⁸ But one can imagine other examples.

Another example or framing of indirect medical harm is where the drug, intentionally or not, removes the probability or cost of perceived *disincentives* that would usually deter the behavior. In choosing which activities to engage in, individuals balance a complex range of costs and benefits. Driving a car at 40 m.p.h. for example, brings costs and benefits. Costs include financial burdens and the risk of collision and concomitant harms. Driving a car at 70 m.p.h. may increase the benefits—you get where you need to go faster—but increases the costs and risks. Thus, individuals might choose the former behavior, but not the latter. However, reducing the costs of driving at 70 m.p.h.—for example, by driving when no cars are on the road, reducing the risk of collision—will alter the relative balance of costs and benefits, making

45. For example, the questions implicated in statutory and constitutional standing together can mostly be boiled down to considerations regarding the nature of the injury (concrete and particularized), its causal connection to the complained of conduct, and the zone of interests' test.

46. Some may argue that the line between direct promotion and a removal of disincentives is a thin one. Erectile dysfunction, they might argue, is better understood as a disincentive to intercourse. I do not in principle oppose this argument.

47. For example, it is unclear whether Viagra recipients would engage in increased intercourse even without the drug, resulting in a high degree of STDs anyway. Frederik Joelving, *Viagra-Popping Seniors Lead the Pack for STDs*, REUTERS (July 6, 2010, 8:52 AM), <http://www.reuters.com/article/us-viagra-stds-idUSTRE6652HP20100706> [<https://perma.cc/CRE4-EE93>].

48. Madonna Behen, *Drugs like Viagra Linked to Higher Rates of STDs*, HEALTHDAY (July 5, 2010), <https://consumer.healthday.com/sexual-health-information-32/homosexuality-news-386/drugs-like-viagra-linked-to-higher-rates-of-stds-640798.html> [<https://perma.cc/7KEJ-L5F8>].

the behavior more attractive. Scholars use the term risk compensation to describe the phenomenon—engaging in risk “based on the expectation that some intervention . . . has decreased . . . exposure to harm.”⁴⁹

An increase in risky behavior can occur for two reasons. First, the intervention might reduce the *probability* of the disincentive from occurring. Condomless sexual behavior brings major risks such as that of HIV transmission and pregnancy. But pills that allow a person to reduce the *probability* of pregnancy or HIV transmission decrease the expected cost of engaging in unsafe sexual behavior, thus increasing the expected amount of the behavior.

Next, medications can reduce the overall *cost* of the disincentive without necessarily affecting the probability of it occurring. There is no equivalent to PrEP to prevent the spread of gonorrhea. But the existence of antibiotics renders the cost of gonorrhea transmission minimal. It may not figure much in the calculation as to whether to wear condoms.⁵⁰ Pills that reduce the harm of HIV, by rendering it a manageable disease, may similarly reduce the perceived cost of contracting HIV.

Let us assume that, were risk compensation not to occur, that the relevant drug decreases the expected harm to some “goal” amount. Risk compensation increases the expected harm above that goal amount. The expected harm can take two forms.

First, the original form of harm may continue to subsist above the goal amount. Thus, assume PrEP or the pill decreases the risk or cost of transmission or pregnancy by two-thirds (the number is closer to 100%),⁵¹ but the individual engages in unprotected intercourse three times more frequently than before. The original type of harm—HIV transmission or pregnancy—will therefore maintain the same impact as before the drug was released.

Second, and in addition, the behavior might introduce *other* forms of harms. Condomless sex would lead to an increase in other STDs. And the costs associated with those harms change over time. For example, with the increase in antibiotic resistance, the costs of bacterial STDs like gonorrhea may greatly increase.⁵²

49. Kristen Underhill, *Risk-Taking and Rulemaking: Addressing Risk Compensation Behavior through FDA Regulation of Prescription Drugs*, 30 YALE J. ON REG. 377, 379 (2013).

50. Jill Blumenthal & Richard H. Haubrich, *Risk Compensation in PrEP: An Old Debate Emerges Yet Again*, 16 AMA J. ETHICS 909, 910 (Nov. 2014) (“Furthermore, there has been an increase in syphilis and gonorrhea rates in [men who have sex with men] across the United States, [much of which is] among HIV-infected people, [perhaps] an unintended consequence of risk compensation associated with greater access to and use of [antiretroviral therapy].”).

51. Joanna V. Theiss, *It May Be Here to Stay, But Is It Working? The Implementation of the Affordable Care Act through an Analysis of Coverage of HIV Treatment and Prevention*, 12 J. HEALTH & BIOMED. L. 109, 119 (2016).

52. Vladimir W. Sentome, *Attacking the Hidden Epidemic: Why a Strict Liability Standard Should Govern the Transmission of Sexually Transmitted Disease*, 2006 U. CHI. LEGAL F. 409, 412.

Empirical evidence of all these causal phenomena is hard to come by. Public health scholars have argued that a decrease in stigma surrounding HIV—part of which is attributable to the availability of HIV therapies—has reduced safe-sex.⁵³ And at least *some* empirical evidence exists of this phenomenon in cases of both the pill and PrEP, though it is far from conclusive.⁵⁴

Of course, risk enhancement or compensation can take place with access to other medication as well in other contexts. Drugs designed to promote good health might lead to an increase in strenuous and risky activities; vaccinations against the human papillomavirus (“HPV”) might also increase risky behavior directly or by removing disincentives.⁵⁵ Other studies have looked at the risk compensation from Lyme disease vaccination.⁵⁶ Nor does risk compensation occur only with drug effects. Child-safe packaging requirements can result in risk compensation, as parents might think that they that they no longer need to keep medications outside children’s reach.⁵⁷ The key principle that defines these harms and on which I will expand in the next Part, is that they are caused, not directly by the drug, but because an intervening cause—the patient, for example—engages in some higher risk behavior because of the drug.

53. See American Health Consultants, *CDC Stats Show Unsafe Sex Practices Are Increasing*, 4 AIDS ALERT 43, 43–45 (1999).

54. See Prior to the FDA’s approval of Truvada, health advocacy groups, including the AIDS Healthcare Foundation, argued that the long-term costs of approving Truvada outweighed its potential benefits. “[T]he AHF argued that the use of Truvada as PrEP would increase ‘risk compensation’ among [men who have sex with men], meaning that users ‘may [forego] highly effective and proven protective measures such as condoms in favor of a ‘magic pill’ that is far less effective.” Jason Potter Burda, *When Condoms Fail: Making Room Under the ACA Blanket for PrEP HIV Prevention*, 52 SAN DIEGO L. REV. 171, 188 (2015) (quoting Citizen Petition from Tom Myers, Gen. Counsel, AIDS Healthcare Found., to the Food & Drug Admin. (Mar. 5, 2012), <https://www.regulations.gov/document?D=FDA-2012-P-0226-0001> [<http://perma.cc/L3C2-LLSW>]); see also Christian Grov et al., *Willingness to Take PrEP and Potential for Risk Compensation Among Highly Sexually Active Gay and Bisexual Men*, 19 AIDS BEHAV. 2234, 2242 (2015) (finding that those who chose to take PrEP were more likely to have receptive condomless anal intercourse, though only ten percent of men who had *not* engaged in condomless anal intercourse said they now would on PrEP, 23 percent reported it would decrease condom use overall, and 14 percent said it would increase their condom use).

55. Coralia Vázquez-Otero et al., *Dispelling the Myth: Exploring Associations between the HPV Vaccine and Inconsistent Condom Use Among College Students*, 93 PREVENTIVE MED. 147, 148–50 (2016) (finding that, in college students who had received the HPV vaccination, there was no correlation with any change in condom use).

56. Noel T. Brewer et al., *Risk Compensation and Vaccination: Can Getting Vaccinated Cause People to Engage in Risky Behaviors?*, 34 ANN. BEHAV. MED. 95, 95–99 (2007).

57. See W. KIP VISCUSI, FATAL TRADEOFFS: PUBLIC & PRIVATE RESPONSIBILITIES FOR RISK 234–42 (1992) (arguing that the implementation of safety caps on aspirin bottles lulled people into a false sense of safety, thereby undermining the utility of the regulation); W. KIP VISCUSI, REGULATING CONSUMER PRODUCT SAFETY 73–80 (1984) (critiquing consumer product safety regulation of child-resistant bottle caps).

In most cases, the FDA does not analyze or attempt to mitigate the indirect harms caused by drugs—though there are some examples when it does. The Food & Drug Administration Amendments Act of 2007, which specifically authorized the FDA to require Risk Evaluation and Mitigation Strategies (“REMS”), expanded this authority. These strategies allow the FDA to require REMS both pre- and post-approval, require additional instructions and training for providers, and labeling.

The REMS for PrEP seek to limit the indirect harms of drug use such as risk compensation. During the advisory committee hearings, FDA personnel emphasized that the “indication must be considered as only part of a comprehensive prevention strategy to reduce the risk of HIV infection, and that other preventive measures [such as condoms] should also be used.”⁵⁸ Indeed, some speculated that risk compensation would not occur, and that PrEP would encourage *less* risky behavior. Being on PrEP involves “ongoing interaction with counselors, provision of HIV testing . . . [;] taking a pill a day provide[s] a reminder, a daily reminder, of risk of HIV.”⁵⁹ The presenters noted that the clinical effectiveness studies revealed no risk compensation behavior.⁶⁰

B. THIRD-PARTY EFFECTS

Regulatory processes generally examine the effect of the drug on the person who ingests it for the treatment of a particular condition. But introducing drugs into an ecosystem can affect third parties or society in general in various ways. Unintended third parties might ingest the drug directly or be affected in other ways if they come into accidental contact with the drug. The ripple effects of helping or harming a specific individual, for example, may affect everyone with whom she comes in contact.

Another example of this dynamic occurs in the case of cost. Drugs that make it easier or cheaper to treat a certain condition can allow resources to be allocated elsewhere. The converse is true, as the case of Hepatitis C drugs shows. In 2013, the FDA approved drugs that cure Hepatitis C, a chronic condition that affects 3 million individuals.⁶¹ The drugs soon became infamous for their price tag—\$1000 per pill for a 12-week course, amounting to \$84,000 per treatment per individual. The relevant FDA committee did not, of course, consider cost.

58. 1 FDA, CTR. FOR DRUG EVALUATION AND RESEARCH, ANTIVIRAL DRUGS ADVISORY COMMITTEE HEARINGS 242 (May 10, 2012) [hereinafter 1 Truvada Hearings]; *see also id.* at 153, 231, 239 (discussing comprehensive counseling need).

59. *Id.* at 112.

60. *Id.* at 76.

61. Jack Hoadley et al., *The Cost of a Cure: Revisiting Medicare Part D and Hepatitis C Drugs*, HEALTH AFF. (Nov. 3, 2016), <https://www.healthaffairs.org/doi/10.1377/hblog20161103.057356/full> [https://perma.cc/K4KG-gVRT].

But Hepatitis C drugs have become a major drain on the health system in the last two years. The Center for Medicare and Medicaid Services recently reported that total drug spending in 2014 was up 11.3 percent for private health insurance, 16.9 percent for Medicare patients, and 24.3 percent for Medicaid patients, and noted that Hepatitis C drugs played a role in each context.⁶² Overall national spending on drugs was up by about ten percent, partially due to new drug treatments for Hepatitis C.⁶³ In all, \$18 billion in 2014 and 2015 combined was devoted to these drugs, of a total of \$24 billion of increased spending on drugs overall.⁶⁴ Such costs are historically unprecedented.⁶⁵

This increase in spending has ramifications for various third parties. It increases the premiums for private insurance, and the bill for the taxpayer. More importantly, however, it has ramifications for others in public insurance systems. As an analysis from two prominent health institutions notes, pricing the drug at that level will raise the question of “whether or not cuts will be made to education and transportation funds in state and federal budgets, what other health care services we will provide less of, and where patients and payers will find the money they need to access the drug.”⁶⁶ In a world of zero sum budgets, giving some individuals the benefit of the drug will harm the benefits others can get. But the FDA does not take into account any of these considerations.⁶⁷

Notably, the Trump administration has recently taken steps to curb the price of drugs—albeit not Hepatitis C drugs. As FDA Commissioner Scott Gottlieb notes, the FDA “do[es]n’t have the authority to regulate prices, [it does] have the authority—and the responsibility—to” promote competition.⁶⁸ The FDA has therefore prioritized approval of generic competitors to existing

62. *Id.*

63. MURRAY AITKEN ET AL., *MEDICINES USE AND SPENDING IN THE U.S.: A REVIEW OF 2015 AND OUTLOOK TO 2020*, at 1–6 (2016), <https://morningconsult.com/wp-content/uploads/2016/04/IMS-Institute-US-Drug-Spending-2015.pdf> [<https://perma.cc/RH4A-H82T>].

64. *Id.*

65. See Margot Sanger-Katz, *Why the Price of Sovaldi is a Shock to the System*, N.Y. TIMES (Aug. 6, 2014), <http://www.nytimes.com/2014/08/07/upshot/why-the-price-of-sovaldi-is-a-shock-to-the-system.html> [<https://perma.cc/3FMW-WSLQ>].

66. Laura Fegraus & Murray Ross, *Sovaldi, Harvoni, and Why It's Different this Time*, HEALTH AFF. (Nov. 21, 2014), <http://healthaffairs.org/blog/2014/11/21/sovaldi-harvoni-and-why-its-different-this-time> [<https://perma.cc/XVK9-5YQW>].

67. See *Frequently Asked Questions about CDER*, FDA, <https://www.fda.gov/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/faqsaboutcder/#16> [<https://perma.cc/8K2F-MNSU>] (“We understand that high drug prices have a direct impact on patients—too many American patients are priced out of the medicines they need. However, FDA has no legal authority to investigate or control the prices set by manufacturers, distributors and retailers.”).

68. Scott Gottlieb, *Reflections on a Landmark Year for Medical Product Innovation and Public Health Advances and Looking Ahead to Policy in 2018*, FDA VOICES (Jan. 9, 2018), <https://www.fda.gov/NewsEvents/Newsroom/FDAVoices/ucm611998.htm> [<https://perma.cc/D2XJ-HB5H>].

drugs in various ways, setting new records for speed,⁶⁹ with the acknowledged goal of reducing the price of drugs.⁷⁰

Other examples of third-party effects abound. The effects of risk compensation can affect social norms more generally. PrEP, for example, has been linked to evolving social norms regarding condom use.⁷¹ If PrEP transforms norms among communities where condoms were often used, so that people stop using condoms, then individuals not on PrEP may well feel pressured not to use condoms, as commentators at the advisory committee hearings noted.⁷² This, in turn, might put them at risk.

The FDA considers the effects on third parties in some contexts, generally where Congress provides specific instructions to the FDA. Thus, in making special children's packaging for drugs, the FDA followed the requirements laid out by the Poison Prevention Packaging Act of 1970 ("PPPA")⁷³ to avoid harms to third parties (bystanding children). Similarly, the NEPA requires environmental statements for certain drugs. Many drugs produce environmental effects, flowing into groundwater and entering our

69. Michael Mehzer, *FDA on Pace for Record Generic Approvals in 2018*, REG. FOCUS (Sept. 4, 2018), <https://www.raps.org/news-and-articles/news-articles/2018/9/fda-on-pace-for-record-generic-approvals-in-2018> [<https://perma.cc/6296-M6LR>].

70. Describing the steps the FDA has taken is beyond the scope of this Article. They are described in some detail in Kathleen Craddock, Note, *Improving Generic Drug Approval at the FDA*, 7 MICH. J. ENVTL. & ADMIN. L. 421 (2018). See also MANUAL OF POLICIES AND PROCEDURES, CTR. FOR DRUG EVALUATION AND RESEARCH 3–4 (2017), available at <https://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/UCM407849.pdf> [<https://perma.cc/M2KM-XHXL>] (setting out prioritization standards for generics that would increase competition).

71. Liz Highleyman, "Raw Sex": *Are the Rules Changing?*, THEBODY (Dec. 5, 2013), <https://www.thebody.com/article/raw-sex—are-the-rules-changing> [<https://perma.cc/W47R-P44U>]; see also Rod Knight et al., *Complex and Conflicting Social Norms: Implications for Implementation of Future HIV Pre-Exposure Prophylaxis (PrEP) Interventions in Vancouver, Canada*, PLOS ONE, Jan. 12, 2016, at 1, 5–8.

72. 1 Truvada Hearings, *supra* note 58, at 262.

73. 15 U.S.C. § 1471 (2012).

food chain.⁷⁴ The FDA requires a statement in only some cases.⁷⁵ While such impact statements are rare, they do occur.⁷⁶

Another prominent example of the FDA's work in the area is in antibiotic resistance. The overprescription of antibiotics has led to resistant bacterial strains that present grave public health dangers. Although administering a drug would likely help a specific patient, it might also lead to the development of resistant bacteria that can wreak great harm in the long run.⁷⁷

The FDA regulated antibiotic resistance by attempting to limit the overprescription of antibiotics. For example, when the FDA issued a regulation prohibiting the extralabel use of certain antibiotics in 1996, it explained that extralabel use was "capable of increasing the level of drug resistant . . . pathogens" that affect humans, and therefore should be limited. This, the FDA concluded, was an "adverse event" because it presented a "risk to the public health."⁷⁸ The considerations here were both third-party focused—to save undetermined lives who might suffer from antibiotic resistant bacteria—and on indirect harms, as the harm is not immediately caused by the antibiotic. Rather, other biological processes react to the antibiotic, creating the problem. The issue is precisely that the antibiotic will go from being effective in killing bacteria to no longer having any direct effects.

C. NON-HEALTH EFFECTS

Drug approvals can have effects that are non-physiological—indeed, non-health—in nature. The extra costs of Hepatitis C, for example, can lead to opportunity costs with respect to other kinds of government spending such as transportation. But perhaps the clearest (and most controversial) examples

74. Oliver A.H. Jones et al., *Aquatic Environmental Assessment of the Top 25 English Prescription Pharmaceuticals*, 36 WATER RES. 5013, 5018–20 (2002); see also Bent Halling-Sørensen et al., *Occurrence, Fate and Effects of Pharmaceutical Substances in the Environment—A Review*, 36 CHEMOSPHERE 357, 358, 365–66 (1998).

75. The guidance for example excludes situations where: (1) "FDA's approval of the application does not increase the use of the active moiety; (2) . . . increases the use of the active moiety, but the estimated concentration of the substance at the point of entry into the aquatic environment will be below 1 part per billion (ppb); (3) . . . does not alter significantly the concentration or distribution of the substance, its metabolites, or degradation products in the environment" FOOD AND DRUG ADMIN., GUIDANCE FOR INDUSTRY: ENVIRONMENTAL ASSESSMENT OF HUMAN DRUG AND BIOLOGICS APPLICATIONS 2 (1998), <https://www.fda.gov/media/70809/download> [<https://perma.cc/F4AW-LV92>].

76. Raanan A. Bloom & John C. Matheson III, *Environmental Assessment of Avermectins by the US Food and Drug Administration*, 48 VETERINARY PARASITOLOGY 281, 282 (1993).

77. See National Institute of Health, *Stop the Spread of Superbugs: Help Fight Drug-Resistant Bacteria*, NEWS HEALTH (Feb. 2014), <https://newsinhealth.nih.gov/issue/feb2014/feature1> [<https://perma.cc/GB7Q-8HGH>] ("[I]n recent decades, antibiotics have been losing their punch against some types of bacteria. In fact, certain bacteria are now unbeatable with today's medicines. Sadly, the way we've been using antibiotics is helping to create new drug-resistant 'superbugs.'").

78. Extralabel Drug Use in Animals, 61 Fed. Reg. 57,732, 57,738 (1996).

of the consideration of non-health effects are situations when moral and political values appear to intrude in the drug approval process.

The last two decades present some interesting examples. The period's "[f]irst political drug approval" was RU486, the so-called abortion-pill. The drug prevents the implantation of an embryo and is also taken to induce a medical abortion within the first few weeks after conception.⁷⁹ The saga of the drug's approval and the FDA's behavior evinces political and value-laden behavior on both sides of the political aisle.⁸⁰

The drug was first approved in France in 1988. In 1989, the FDA approved a policy that allowed individuals to bring drugs from abroad into the country for their personal use.⁸¹ But apparently responding to pressure from Congress,⁸² the FDA prohibited the import of RU486.⁸³ A district court found this decision "based not [on] any bonafide concern for the safety of users of the drug, but on political considerations."⁸⁴ In congressional hearings, George H.W. Bush's FDA Commissioner claimed "that the agency probably knew without contacting [scientists working on RU486] some of the potential risks and benefits with respect to th[e] product,"⁸⁵ prompting the committee chairman to observe that the FDA was "basically offering management by intuition to the American people."⁸⁶

The next year, on the second day of his presidency, Bill Clinton directed the FDA to rescind the import ban on RU486.⁸⁷ However, the holder of the patent could find no manufacturer for the drug, delaying its approval by three years. And the new FDA Commissioner's confirmation was denied—until she assured Republican leaders that she would not actively facilitate the final

79. James G. Dickinson, *Mifeprex: FDA's First "Political" Drug Approval*, 35 MED. MKTG. & MEDIA, Nov. 2000, at 14.

80. Lars Noah, *A Miscarriage in the Drug Approval Process?: Mifepristone Embroils the FDA in Abortion Politics*, 36 WAKE FOREST L. REV. 571, 572-74 (2001).

81. See FDA, REGULATORY PROCEDURES MANUAL, Ch. 9 (1997), https://web.archive.org/web/20030802233153/http://www.fda.gov/ora/compliance_ref/rpm/default.htm; Peter S. Reichertz & Melinda S. Friend, *Hiding Behind Agency Discretion: The Food and Drug Administration's Personal Use Drug Importation Policy*, 9 CORNELL J.L. & PUB. POL'Y 493, 493-94 (2000).

82. Mark A. Hernandez, *RU-486; Safe? Effective? Banned! Why Would the Food and Drug Administration Ban a Drug with Such Potential?*, 11 PENN ST. INT'L L. REV. 653, 671 (1993).

83. "[O]n June 6, 1989, the FDA issued Import Alert 66-47, the basis for the seizure in this case. The alert stated that RU486 was subject to 'automatic detention' and the agents should '[a]utomatically detain all shipments of unapproved abortifacient drugs.'" *Benten v. Kessler*, 799 F. Supp. 281, 286 (E.D.N.Y. 1992).

84. *Id.* But see *Benten v. Kessler*, 505 U.S. 1084, 1085 (1992) (per curiam) (affirming a stay on the district court's injunction against the FDA's ban).

85. *RU486: The Import Ban and Its Effect on Medical Research: Hearing Before the Subcomm. on Regulation, Bus. Opportunities, and Energy, of the House Comm. on Small Bus.*, 101st Cong. 38 (1990) (noting the reasons the FDA gave for the ban) (statement of Ronald Chesemore).

86. *Id.* at 43 (statement of Chairman Wyden).

87. Memorandum on Importation of RU-486, 29 Weekly Comp. Pres. Doc. 89 (Jan. 22, 1993), <https://www.govinfo.gov/content/pkg/WCPD-1993-01-25/pdf/WCPD-1993-01-25-Pg89.pdf> [https://perma.cc/47S3-P3VS].

approval of the drug.⁸⁸ The FDA did, ultimately, fast track the drug's approval, under a regulation that allowed it to do so when a "serious or life-threatening illness" is involved, by claiming that "unwanted *pregnancy*" fell into this category.⁸⁹

The RU486 saga was quickly followed by drama over Plan B during the George W. Bush and Obama administrations. Plan B is a contraceptive that operates before fertilization by, inter alia, hindering ovulation. Advocates sought to render the drug an over-the-counter ("OTC") medication. The FDA (initially) issued a denial over the advice of numerous advisory committees. As a court later found, this outcome by "the agency's senior decisionmakers . . . rest[ed] on improper concerns about the morality of adolescent sexual activity."⁹⁰ This and other concerns, such as those over parental control, became evident in a subsequent GAO Report which concluded that the FDA had behaved unusually in denying OTC status to Plan B.⁹¹ Notably, the Commissioner had appointed individuals such as David Hager, a religious fundamentalist and vocal pro-lifer, to the FDA's Reproductive Health Drugs Advisory Committee, where he voted against OTC status and championed a citizen petition from the group Americans United for Life.⁹²

Lest I seem to suggest that it is solely social conservatives who seek to deploy value judgments in FDA processes, the approval of the heart medication BiDil, presents a counterexample.⁹³ This drug was approved to

88. See Judy Mann, *We Need the Abortion Pill Now*, WASH. POST (June 23, 2000), <https://www.washingtonpost.com/archive/lifestyle/2000/06/23/we-need-the-abortion-pill-now/d5190008-9de6-4d77-acd5-71af382e8b73> [https://perma.cc/GND6-HBGM]; Katharine Q. Seelye, *House Votes to Block FDA on Approval of Abortion Pill*, N.Y. TIMES (June 25, 1998), <https://www.nytimes.com/1998/06/25/us/house-votes-to-block-fda-on-approval-of-abortion-pill.html> [https://perma.cc/3LGK-7QAT].

89. See New Drug, Antibiotic, and Biological Drug Products; Accelerated Approval Procedures, 57 Fed. Reg. 58,942, 58,958 (Dec. 11, 1992) (codified as amended at 21 C.F.R. pt. 314(H)); see also PRESCRIBER'S AGREEMENT FORM, U.S. FOOD AND DRUG ADMINISTRATION, CENTER FOR DRUG EVALUATION AND RESEARCH (2001).

90. *Tummino v. Von Eschenbach*, 427 F. Supp. 2d 212, 233 (E.D.N.Y. 2006).

91. FOOD AND DRUG ADMIN., DECISION PROCESS TO DENY INITIAL APPLICATION FOR OVER-THE-COUNTER MARKETING OF THE EMERGENCY CONTRACEPTIVE DRUG PLAN B WAS UNUSUAL 7-11, 42-46 (2005), available at <http://www.gao.gov/new.items/do6109.pdf> [https://perma.cc/7K58-VJWV] (providing timeline of internal FDA actions on the Plan B OTC switch application); *id.* at 51-52 (incorporating a memorandum from the Director of the Office of New Drugs noting moral concerns regarding adolescent sexual activity and parental control raised by the Plan B OTC switch application).

92. Rick Weiss, *New Status for Embryos in Research*, WASH. POST, Oct. 30, 2002, at A1.

93. Note, of course that sometimes liberal administrations appear to have similar priorities. The Obama HHS arguably treated Plan B no better than the Bush administration. Lisa Heinzerling, *The FDA's Plan B Fiasco: Lessons for Administrative Law*, 102 GEO. L.J. 927, 938-39 (2014).

treat cardiac failure in African Americans, and was the first drug to be targeted to a specific racial group.⁹⁴

The fundamental question in the BiDil approval story was not safety and efficacy, which was already established. Rather, what was at issue was social policy about race more generally. First, there was the question of the impact on racial health equity. Some “influential black political and scientific groups embraced BiDil . . . as a way to redress years of inequality in medical treatment and outcomes.”⁹⁵ The trials for BiDil included a large cohort of African-Americans as the result of intensive recruitment.⁹⁶ In a world where African-Americans were traditionally underrepresented in clinical trials, often due to poor recruitment, racialized medicine offered some benefits.

On the other hand, racial health inequity mostly has structural causes.⁹⁷ And as Dorothy Roberts observes, such “racial medicine” can divert attention away from these root causes “toward genetic explanations and technological solutions.”⁹⁸ Popularizing racialized medicine can thus exacerbate bad health among minorities.

More generally, even if the drug worked better for one race than another, “critics said that endorsing a drug for one race gave official government imprimatur to the discredited notion of race as a biological category.”⁹⁹ Without such affirmation, racial categories remained fluid. As one witness before the FDA Advisory Committee asked: “Who is African-American? . . . Are we going to allow people to self-identify? Is the physician going to be the one that says you are black? . . . Are there going to be criteria, national standardized criteria for how people identify individuals for the treatment of

94. Stephanie Saul, *FDA Approves Heart Drug for African-Americans*, N.Y. TIMES (June 24, 2005), <https://www.nytimes.com/2005/06/24/health/fda-approves-a-heart-drug-for-african-americans.html> [<https://perma.cc/E2J7-328G>].

95. *Id.* Dorothy Roberts observes of this tension, “‘Is race-based medicine good for us?’ is at once a medical and political question, and the answer depends on one’s approach to achieving racial equality. There is no consensus among African Americans on this question.” Dorothy E. Roberts, *Is Race-Based Medicine Good for Us?: African American Approaches to Race, Biomedicine, and Equality*, 36 J.L. MED. & ETHICS 537, 538 (2008).

96. See Sharona Hoffman, ‘Racially-Tailored’ Medicine Unraveled, 55 AM. U. L. REV. 395, 402 (2005); see also Britt M. Rusert & Charmaine D.M. Royal, *Grassroots Marketing in a Global Era: More Lessons from BiDil*, 39 J.L. MED. & ETHICS 79, 81–82 (2011).

97. Roberts, *supra* note 95, at 542.

98. *Id.*

99. Saul, *supra* note 94; see also Howard Brody & Linda M. Hunt, *BiDil: Assessing a Race-Based Pharmaceutical*, 4 ANN. FAM. MED. 556, 557 (2006); Erik Lillquist & Charles A. Sullivan, *Legal Regulation of the Use of Race in Medical Research*, 34 J.L. MED. & ETHICS 535, 536 (2006); Dorothy E. Roberts, *Law, Race, and Biotechnology: Toward a Biopolitical and Transdisciplinary Paradigm*, 9 ANN. REV. L. & SOC. SCI. 149, 150 (2013); Carolyn Johnson, *Should Medicine Be Colorblind?: Debate Erupts Over a Drug That Works Better in African-Americans*, BOS. GLOBE (Aug. 24, 2004), http://archive.boston.com/news/globe/health_science/articles/2004/08/24/should_medicine_be_colorblind [<https://perma.cc/W6UX-NC26>].

BiDil?”¹⁰⁰ Even more problematic, the scientific validity of such categories was, and remains, dubious: There is so much variation within racial categories that biological race is a poor predictor for medical outcomes. As one scientist put it, “[y]ou might as well sort people by height.”¹⁰¹ In this situation in particular, the drug was designated for *self-identified* African-Americans, which would exacerbate inaccuracies. Indeed, the science is all the more problematic given that the trials never *included* other races except for self-identified African-Americans.¹⁰² The generic components of BiDil had long been used to treat medication among people of all races.

Drugs therefore implicate important values that play a role in the approval process. It is important to consider whether and how to incorporate these considerations within the process.

D. SHORTCOMINGS

As my examples above show, the FDA *does*, sometimes, take into account effects that are non-physiological. However, such assessments are often *sui generis*, or not carried out in a way that is systematized, clear, and cogent. As a result, physiological concerns tend to dominate.

For example, a review of the PrEP hearings shows shortcomings in various areas, including (a) a failure to obtain clear data regarding non-physiological effects; (b) a failure to assess and analyze the empirical and ethical implications of the data that was made available; (c) a failure to adjust the process so that assessments of this non-physiological data could be taken into account; and (d) a failure to extent a similar review in other contexts.

1. Lack of Collection of Data or Assessment of Concerns

First, data on non-physiological effects such as risk-compensation had just not been collected. As presenters themselves had noted, the lack of risk compensation in the studies probably reflected the “enormous amounts of risk reduction counseling that people received and the condoms” as part of the study.¹⁰³ Thus, it was hard to draw any conclusions.

Next, when data or concerns *were* presented, there was limited assessment, both empirical or ethical. For example, several nurses, who specialized in HIV care, commented on the proceedings. They were nearly

100. 2 FDA, CTR. FOR DRUG EVALUATION AND RESEARCH, CARDIOVASCULAR AND RENAL DRUGS ADVISORY COMMITTEE HEARINGS ON APPROVAL OF BIDIL 250 (2005) [hereinafter BiDil Hearings].

101. Abigail Zuger, *From Bang to Whimper: A Heart Drug's Story*, N.Y. TIMES (Dec. 24, 2012), <https://www.nytimes.com/2012/12/25/science/from-bang-to-whimper-a-heart-drugs-story.html> [<https://perma.cc/QJ3J-HGNV>].

102. BiDil Hearings, *supra* note 100, at 60; *see also* Shiloh Krupar & Nadine Ehlers, *Biofutures: Race and the Governance of Health*, 35 ENV'T & PLAN. D: SOC'Y & SPACE 222, 223 (2017); Osagie K. Obasogie, *The Return of Biological Race: Regulating Innovations in Race and Genetics Through Administrative Agency Race Impact Assessments*, 22 S. CAL. INTERDISC. L.J. 1, 4 (2012).

103. 1 Truvada Hearings, *supra* note 58, at 76.

unanimous in their opinion that risk compensation would be a serious problem.¹⁰⁴ They cited studies in which a sizeable number of respondents acknowledged that they would stop using condoms were PrEP widely available.¹⁰⁵ But the implications were never discussed.

Two other public commenters were concerned by cost, but members never discussed their concerns. As one commenter explained, ensuring that someone who lived with HIV took the drug would reduce transmission as their viral load would be reduced.¹⁰⁶ Ensuring more people with HIV took the drug would therefore reduce transmission far more than giving the drug to someone who *may* or *may not* encounter someone who was HIV positive. To get the same effect, one would have to spend a lot more money.¹⁰⁷ However, their concerns were never discussed. Yet another commenter discussed how PrEP would change the norms of condom use: “[I]t will make it even harder for people, especially women, to” negotiate condom use with their partners to “protect themselves.”¹⁰⁸ That concern was also unaddressed.

As importantly, the *ethical* aspects of risk compensation were never assessed. A couple of commenters noted that risk compensation concerns were paternalistic: “[C]lients are capable of making healthy decisions for their own lives [and] . . . don’t require our paternalizing them.”¹⁰⁹ This was a valid response but was left unaddressed by committee members.

Thus a representative of the AIDS Health Foundation did not exaggerate when he complained on the second day of the hearings that “[t]estimonials on risk compensation, and cost . . . were all but ignored.”¹¹⁰ Apart from passing observations noting the lack of data on risk compensation early on in the proceedings, the members of the committee ignored most non-physiological concerns. This is hardly surprising: Apart from a solitary social worker, the committee consisted of medical doctors and researchers with advanced degrees in biology and chemistry (and no nurses).¹¹¹

104. *Id.* at 262; *see also id.* at 264, 265, 269, 330–31 (“Using this treatment as a preventive measure for HIV will be seen as a medical condom.”).

105. *Id.* at 262.

106. Those with suppressed viral loads are unable to transmit the virus. *10 Things to Know About HIV Suppression*, NAT’L INST. ALLERGY & INFECTIOUS DISEASES (Nov. 14, 2017), <https://www.niaid.nih.gov/news-events/10-things-know-about-hiv-suppression> [<https://perma.cc/YDM8-UT2K>].

107. 1 Truvada Hearings, *supra* note 58, at 282–83, 318 (“[Far more than ensuring] this means the cost of preventing just one HIV infection over one-year period of time will be well over \$500,000. This figure is approximately 20 times higher than the cost of treating an HIV-positive person for one year.”).

108. *Id.* at 322.

109. *Id.* at 341–42, 509–10 (“[H]aunted by a certain specter of what I would characterize as maybe an undercurrent of anger and fear at people who don’t or can’t or won’t use condoms” and recommending “patient empowerment.”).

110. *See* 2 FDA, CTR. FOR DRUG EVALUATION AND RESEARCH, ANTIVIRAL DRUGS ADVISORY COMMITTEE HEARINGS 197 (May 11, 2012).

111. 1 Truvada Hearings, *supra* note 58, at 2–12.

2. Failure of Process to Incorporate Data into Concerns

Next, members of the committee noted that even if members had concerns on non-physiological effects on the patients taking the drug, such as the development of viral resistance among third parties, the voting process did not systematically incorporate those concerns. As one member noted, “the vote, to a certain extent, hinges on what the REM[S] looks like” but complained that the committee could not make their vote conditional on “chang[ing] the REM[S].”¹¹² Another member similarly criticized the all-or-nothing choice: “I just don’t think it’s a good logic to say, our choice is either don’t approve and let them use it off-label, or approve it with something we know is not going to be very effective in actually changing behavior.”¹¹³ The members sought “good data about what’s going on” with respect to non-physiological criteria not based on “voluntary [self-]assessment.”¹¹⁴ But given that the only systematic data available was on physiological side-effects and effectiveness, members appear to have voted on that basis.

3. Lack of Systematization Across Drugs

Finally, the PrEP committee did not follow a systematic assessment of the kinds of harms across drugs. Indeed, Dr. Susan Buchbinder, a presenter in the PrEP committee hearings joked about this fact: When it comes to statins, for example, there “hasn’t been a lot of concern about risk compensation. We’re not asking people, are people who are on statins going to be eating more ice cream?”¹¹⁵ Notably, the question of risk compensation came up in another case—approval of Plan B, where the FDA *did* review numerous risk compensation studies to determine whether the approval would result in higher sexual activity (and greater STI contraction) in adolescent women. “Reviewers analyzed the actual use data as well as data from five other studies” cumulatively with “more than 11,000 enrollees” and found no appreciable risk compensation behavior.¹¹⁶

Even when it comes to a specific concern—risk compensation—the FDA’s behavior varies across drugs. Some of the other harms to which I alluded to above—packaging for children or environmental impact—are congressionally mandated instructions rather than any systematic effort by the FDA to assess third-party effects.

112. *Id.* at 440, 505 (statement of Member Padian).

113. *Id.* at 482 (statement of Member Morrato).

114. *Id.* at 470 (statement of Member Padian).

115. *Id.* at 49.

116. *Tummino v. Torti*, 603 F. Supp. 2d 519, 531 (E.D.N.Y. 2009); *see also id.* at 528 (“[T]he results of the AUS [actual use study] demonstrated that the frequency of unprotected sex did not increase, condom use did not decrease, and the overall use of effective contraception did not decrease [with use of Plan B].” (second and third alterations in original) (quoting Defendant’s Exhibit)).

As a result, when the FDA engages in these kinds of assessment, it creates the danger that it has to do more with unstated political agendas and special interests—concerns around children—for example, then a systematic assessment. Why indeed, one might ask as Dr. Buchbinder did, are we so concerned with risk compensation involving an HIV drug but not when it comes to statins—might HIV stigma be the answer? And why do non-health concerns suddenly become an issue when a drug involves a certain racial minority or women’s reproduction?

The key here is to admit that our concerns about drugs collateral effects are not limited to their unintended physiological effects on their recipients. Rather, drugs, like other medical phenomena, have ramifications that extends beyond their immediate physiological effect into the social realm. Understanding and categorizing these effects, working out when, and why we should take them into account, are important to addressing these concerns explicitly.

IV. THE ETHICAL CASE FOR CONSIDERING ‘OTHER’ SIDE-EFFECTS

The categories I lay out above are somewhat fuzzy and unelaborated. In what follows, I more fully flesh out my understanding of indirect harms, group harms, and non-health effects, and the ethical issues they raise. As I explain, ethical considerations do not undermine, and indeed, may justify, the consideration of other side-effects. As ethical considerations undergird legal policy, especially around medical research and practice, they are an important precursor to additional policy considerations.

A. INDIRECT HARMES

The first question concerns whether only direct effects or indirect effects of a particular health decision should be taken into account in FDA decisionmaking. The first task is to distinguish between direct and indirect harms.¹¹⁷

There are two approaches to this distinction. The first is the “purpose” approach, which bioethicist Dan Brock advocates. Brock explains: “[T]he direct benefit[] of opening a large, new primary care clinic [is] the improved primary health care . . . the consequence that the hospital’s cafeteria is no

117. Samuel J. Rascoff & Richard L. Revesz, *The Biases of Risk Tradeoff Analysis: Towards Parity in Environmental and Health-and-Safety Regulation*, 69 U. CHI. L. REV. 1763, 1771 (2002) (“[T]he very act of regulating the target risk itself brings about ancillary risks.”). The authors proceed to give examples, but don’t expand beyond that definition, apart from acknowledging later that any substitution effects, where an entity substitutes one harmful substance for another, “is more mediated.” *Id.* at 1775. Substitution effects are likely mitigated in the drug context given the FDA’s control over approval.

longer unprofitable . . . is an indirect benefit, even if it may be as closely causally related.”¹¹⁸

But this approach seems somewhat counterintuitive. Imagine two scenarios. Under the first, I ask my nurse to tell my doctor to talk to the pharmacist who adjusts my course of medication per my wishes. Under the second, I talk to the pharmacist, and achieve the same result. It seems fair to say that the latter approach achieved the same goal as the former, but more directly. Directness here is clearly not measured by goal.

Indeed, measuring directness by purpose would collapse all side-effects into indirect effects. Whether a purpose is a side-effect or a target effect is generally determined by the purpose of the drug.¹¹⁹ Any effect of a drug that is not intended would therefore be both a side- and an indirect-effect.

The better alternative is the causal approach. Tort law uses this approach, for example, to determine proximate causation. In inquiring whether a cause is proximate enough to be tortious, a minority of jurisdictions use what is called the direct causation test. Under that test, a cause is indirect if it is separated from an effect by an intervening cause. This intervening cause must (1) be independent of the original act, (2) be a voluntary human act or an abnormal natural event, and (3) occur in time between the original act and the effect.¹²⁰

To take a few examples: The risk compensation behavior that comes from PrEP would be an example of an indirect harm of administering the medication. Condomless sex would be an independent, voluntary, and intervening behavior of various individuals which could result in increased non-HIV STD transmission. Similarly, the effects of expensive Hepatitis C drugs on the availability of other forms of care or state spending will be indirect. The expense of the drug will trigger a range of other independent decisions on where to cut costs because of the high cost of the drug. In contrast, the harm BiDil opponents point to, appears direct. The expressive racial offense and categorization occurs at the time of approval and is reinforced anytime anyone takes the drug because they are African-American.

Even under my definition, however, one might argue that considering indirect effects violates bioethical principle. For example, imagine that a doctor and murderer are both fatally ill, and there is only enough of a drug to save one person. The doctor, if saved, would heal numerous people; the murderer would kill again.¹²¹ Still, valuing people based on what they can

118. Dan W. Brock, *Separate Spheres and Indirect Benefits*, 1 COST EFFECTIVENESS & RESOURCE ALLOCATION, Feb. 2003, at 4.

119. As in the regulatory context. See, e.g., Rascoff & Revesz, *supra* note 117, at 1766–67.

120. See 21 PERSONAL INJURY—ACTIONS, DEFENSES, DAMAGES § 101.06 (2019); Tampa Elec. Co. v. Jones, 190 So. 26, 27 (Fla. 1939).

121. The example is mine, the reasons are Brock's. See generally Brock, *supra* note 118 (describing the distinction between direct and indirect benefits). Brock lays these out as three reasons, but they effectively boil down to two. *Id.* He presents the equality claim as two separate

provide society treats them as means (to these other purposes) and therefore violates the Kantian approaches that dominate bioethical reasoning. Accordingly, some argue, individuals should be given access to the resource equally. A better system would be to give them both an equal *chance* to get access to the medication—for example, through a lottery system.¹²²

This position merits two responses. First, many would argue that Kant, himself, would seek to choose among the doctor and murderer based on a theory of moral desert. While the consequentialist would choose the doctor because she cares about effects, Kant might pick among them because of their past behavior. Similarly, someone who subscribes to the principle “priority for the worse-off” would see the sicker of the two as more deserving of treatment. A luck egalitarian would provide treatment to the patient who is least to blame for her illness.¹²³ Exponents of other ideologies might tell the FDA not to consider indirect effects, but rather, other moral criteria when making decisions. Which illness has the “sickest” people; which group of patients or manufacturers are the most morally deserving. These criteria, however, are better relegated to “non-health” related considerations that I raise in the final Section.

Suffice it to say, however, that whatever one’s predilections, consequentialism is a sufficiently dominant form of ethical reasoning that its touchstone—indirect effects of a drug—is a plausible parameter for FDA reasoning in this context. It does not, at least, present an ethical bar for the FDA to take into account these effects.¹²⁴

The second response concerns the great complexity of our healthcare system that makes such consequentialist, indirect-effect based reasoning inevitable. Let us say that Medicaid allocates a certain set of resources to Hepatitis C treatment. This will indirectly affect those in need of, say, diabetes medication because social resources are finite. Thus, we must respect the

claims: Treating people differently disrespects their equal moral worth as humans. *Id.* at 7. Second, it disregards their “equal moral claims” as human beings to obtaining health rights. *Id.*

122. Equity here can differ based on various approaches. We might say that all individuals deserve an equal amount of the benefit. Alternatively, we might say that equity demands that the worse off should get more of the benefit. For a full discussion of the equity considerations that these so-called egalitarian versus prioritarian approaches raise, see generally R. George Wright, *Equal Protection and the Idea of Equality*, 34 L. & INEQ. 1 (2016) (discussing equity considerations). See Dan W. Brock, *Health Resource Allocation for Vulnerable Populations*, in *ETHICAL DIMENSIONS OF HEALTH POLICY* 283 (Marion Danis et al. eds., 2002).

123. Indeed, Brock engages in a sleight of hand. In critiquing effects-based reasoning, he takes as a premise moral theories that deny the moral relevance of effects based reasoning. Brock, *supra* note 118, at 5–9. Consequentialism, which accepts effects-based reasoning, is, per his assumptions, made irrelevant. But of course, when the chosen moral theory or theories treat effects as irrelevant, it is hardly surprising when effects in fact prove to be irrelevant.

124. Note if the FDA bans the drug altogether, there are no equity issues. All individuals would be treated alike; none would have access to the drug. Nor would we treat individuals as means. Rather the denial would be based not on the behavior of specific individuals, but on social effects as a whole.

principle of equal worth, not just among potential Hepatitis C patients, but *between* potential Hepatitis C and diabetes patients: Individuals in both groups have equal worth. Medicaid would have to consider and adjust for the likely indirect effects of allocating resources to one drug over another.

To put it more starkly, assume the doctor had Hepatitis C and the murderer had diabetes. Let us say that a decisionmaker allocates the Hepatitis C drug (sofosbuvir) for the doctor. Future decisionmakers would have to decide whether and how to allocate diabetes drugs to the murderer given that the allocation of sofosbuvir to the doctor depleted resources. Thus, when deciding whether to allocate sofosbuvir to the doctor in the first place, the original decisionmaker should consider the equal claim of the diabetes patient. Some consequentialism seems inevitable in the *allocational* context.

B. THIRD-PARTY EFFECTS

Third-party harm occurs when the drug is prescribed for use, and actually used by person A, but person B is harmed by the use either directly or indirectly.¹²⁵ Those harmed by secondhand smoke suffer direct third-party harms; those affected by antibiotic resistance suffer indirect third-party harms. The primary purpose of the FDA's regulation of side-effects has been to protect the recipient of the drug, person A, from harm. Approval only occurs if the benefit of the drug to its recipient outweighs its cost to her.¹²⁶

In considering the duties the FDA might owe to these third parties, it is useful to distinguish between micro-, meso-, and macro-ethics.¹²⁷ Although this set of distinctions does not neatly separate ethical questions, it provides a frame around which to organize our analysis.

Micro-ethics focuses on individual obligations and duties. For example, the duties individual researchers owe specific patients is a micro-level concern. The focus of the FDA has been on the micro-level—on the well-being of the drug recipient herself. However, slowly moving beyond the recipient to meso- and macro-levels invoke an even more complex web of obligations.

Meso-level ethics concern the duties of specific institutions or groups vis-a-vis each other. This includes the duties owed to a particular group of patients, clan, or tribal entity. At the meso-level, there are bonds of obligation

125. I note that *potential* users do not count as third parties. A burglar who steals drugs from a pharmacy is not a third party as there was no primary party to whom his use is incident.

126. One might argue that by limiting the availability of the drug to non-patients by maintaining prescription standards, the FDA does in fact regulate third parties. However, those individuals are not third parties as there is no principal party—a Party A—who is taking the drug in that context.

127. See generally Craig Konnoth, *Health Information Equity*, 165 U. PA. L. REV. 1317 (2017) (considering approaches to justice within limited circumscribed contexts, and then at a more general level beyond that context). This definition maps on to similar approaches in sociological inquiry and political theory as well. JONATHAN H. TURNER, *CONTEMPORARY SOCIOLOGICAL THEORY* 27 (2012); John T. Rourke, *Levels of Analysis*, in *INTERNATIONAL POLITICS ON THE WORLD STAGE* 65 (10th ed. 2005).

between the individual and certain groups that surround her—her family for example. Third-party harms at the meso-level might violate these obligations. The effects of secondhand smoke on family members is one such example.

Macro-level ethics concerns duties owed to entire states, nations, or global entities. Macro-level harms occur at a more systematic level. Because person A received access to medication for Hepatitis C, Medicaid can no longer treat persons B through Z for their less expensive but no less threatening ailments. Antibiotic resistance is an example of a global threat.

As one progresses up from meso to macro levels of analysis, the bonds of obligation seem to loosen. The obligations owed to a stranger that is yet to be born but will suffer from a patient's frequent antibiotic use seem more attenuated than those owed to one's roommate.¹²⁸ Rather, in our society we are more likely to think that those duties are mediated by broader social institutions. The individual may have a responsibility to vote responsibly to ensure an administration that considers harms to all of society as well as to future generations. But we are less likely to think (though of course, some do) that the individual owes a duty directly to those people.

The FDA, we all agree, must engage in micro-ethical analysis by considering the burdens on and duties to the individual who takes the drug. The FDA is also the governmental entity (or at least, one of the entities) that mediates the individual's relationship with the collective at the macro-level. It must consider its responsibilities to the collective, to society in general, when engaging in drug regulatory actions. It should be responsible for enforcing macro-level justice considerations such as equality that take into account the worth and needs of all individuals in society as well as to future societies.

The place where the FDA's intervention seems the most dubious is at the meso-level. Should the FDA adopt a duty of care to the various groups that surround the patient—their family, friends, and other circles of intimates? First, some may say that at the meso-level, visions of the good, rather than the just, govern.¹²⁹ The obligations are those of friendship and love. The FDA's intervention would displace the primary obligations between intimates.

128. The duties owed to strangers is the subject of a rich philosophical debate that I do not plumb in depth here. *See generally* THE ETHICS OF ASSISTANCE: MORALITY AND THE DISTANT NEEDY (Deen K. Chatterjee ed., 2004); Richard Arneson, *Consequentialism vs. Special-Ties Partiality*, 86 *MONIST* 382 (2003); Deen K. Chatterjee, *Moral Distance: Introduction*, 86 *MONIST* 327 (2003); Wendy C. Hamblet, *The Geography of Goodness: Proximity's Dilemma and The Difficulties of Moral Response to the Distant Sufferer*, 86 *MONIST* 355 (2003); Violetta Ionescu, *Distance, Determinacy and the Duty to Aid: A Reply to Kamm*, 20 *L. & PHIL.* 605 (2001) (discussing duties owed to strangers); Frances Kamm, *Does Distance Matter Morally to the Duty to Rescue?*, 19 *L. & PHIL.* 655 (2000); Jan Narveson, *We Don't Owe Them a Thing! A Tough-minded but Soft-hearted View of Aid to the Far Away Needy*, 86 *MONIST* 419 (2003); Peter Singer, *Famine, Affluence, and Morality*, 1 *PHIL. & PUB. AFF.* 229 (1972); Jeremy Waldron, *Who Is my Neighbor?: Humanity and Proximity*, 86 *MONIST* 333 (2003).

129. *See generally* Sarah E.M. Caldwell & Nicholas Mays, *Studying Policy Implementation Using a Macro, Meso, and Micro Frame Analysis: The Case of the Collaboration for Leadership in Applied Health Research & Care (CLAHRC) Programme Nationally and in North West London*, 10 *HEALTH RES. & POL'Y SYS.* 32 (2012) (discussing the potential for misunderstanding and misinterpretation at the meso-level).

Second, some might argue that FDA intervention would displace the obligations that local government bodies owe their citizens.

This second objection I deal with in the final Part. The first objection is not very convincing. The federal government's duty—via its drug regulatory body, namely, the FDA—does not dissipate merely because other bonds of obligation are present. Limiting the FDA's intervention would be harmful where drug recipients do not live up to their obligations to others because they are selfish, amoral, or unable (for example, if they are addicted to a specific drug). And it would be impossible for the FDA to predict and intervene only where private obligations fail. Finally, even at the macro-level there are other bonds beyond the dry dictates of justice. Patriotism, for example, is an emotive bond that supposedly unites groups together. But we do not deny the impracticality and implausibility of relying on such ideals when it comes to government functioning.

Note that the considerations of micro-, meso-, and macro-ethics do not always point in the same direction. The interests of the individual and of those around her might be at loggerheads. In the case of BiDil, for example, some commentators explicitly recognized that the drug could increase racial polarization. But, nonetheless, they apparently felt that the benefits to the individual outweighed the social costs.¹³⁰ One can imagine a range of other examples—Hepatitis C patients would benefit from even an expensive drug, even if others reliant on social services may suffer. Those who have access to PrEP may enjoy the benefits of unsafe sex—but changing norms about safe sex will harm those who do not have access to the medication. Scholars note that if norms about safe sex change, such individuals may feel reluctant to demand condom use.¹³¹

In such cases, the FDA may have to engage in balancing the interests of the individual versus society. This balancing is familiar in judicial and other agency contexts. Ideally, for example, the FDA would have been able to take into account the astronomical cost of the Hepatitis C drug. Under existing law, states are required to provide “medically necessary” care, including available and approved drugs, to their Medicaid population. Individuals have successfully sued to receive access to the treatment post-approval, inevitably

130. Leah Sammons, *Racial Profiling: Not Always a Bad Thing*, CHI. DEFENDER, Feb. 9, 2006; Gary Puckrein, *BiDil: From Another Vantage Point*, 25 HEALTH AFF. w368, w374 (2006).

131. See Burda, *supra* note 54, at 187 (documenting an argument from AHF, the AIDS Healthcare Foundation, who argued “that Truvada’s efficacy must be measured against the ninety-five percent efficacy of proper and regular condom usage”); see also J.L. Peterson et al., *Perceived Condom Norms and HIV Risks Among Social and Sexual Networks of Young African American Men Who Have Sex with Men*, 24 HEALTH EDUC. RES. 119, 122–26 (2009) (finding that men who believed that their friends used condoms, or would approve of them using condoms, were much more likely to use condoms and not engage in other high risk sexual behaviors).

stretching their budgets and limiting coverage.¹³² A more ethical approach might have been to assess the cost to society before approval.

At other times, the interests of the individual and society run together. For example, unsafe sexual norms can ultimately harm even those on PrEP. They may contract other STDs. And as the incidence of HIV in the rest of the population rises, even those who were once on PrEP might contract HIV if their adherence falters or they lose access to the drug—if they lose insurance for example. In such cases, the FDA’s mandate seems much clearer.

C. NON-HEALTH EFFECTS

Drugs might produce direct or indirect effects that are not health related, in the sense of producing physiological effects. The racist message that the approval or prescription of a drug like BiDil produces would be a direct but non-health harm. Similarly, a medication that tastes good produces direct benefits for a patient of a kind that we would not ordinarily call health related. But many non-health harms are indirect—limits to transportation and education, for example, because of the high cost of Hepatitis C drugs.

Two relevant questions arise when determining whether the FDA can consider non-health (i.e., in this case, non-physiological) effects: (1) Should the FDA ethically consider non-health concerns in making its decision?; (2) Can we draw a coherent line to draw between health and non-health concerns?

In previous work, I have taken a position that would appear to militate against the FDA taking into account non-physiological effects. As I have explained, “[e]veryday moral reasoning assesses a particular activity based on the norms of the context or institution in which it is situated—the particular law school, family, or community. We decide if that is ‘the way we do things here.’”¹³³ As theorists such as Michael Walzer argue, the nature, purpose, and shared understandings of a particular social situation—or to use Walzerian terminology, “sphere[] of justice”¹³⁴—help determine the normative import of a particular action. We assess the functioning of the criminal justice system by how well it achieves certain penological goals, of a family by the bonds of love and care that pervade it. It would be strange to flip this approach and assess family functioning by how well wrongdoers in the family are punished, and the criminal justice system by measuring bonds of caring.

Not only would it be strange, I have argued more recently, but it would be dangerous to do so. For example, using the language of consumerism to define healthcare interactions, undermines fiduciary relationship between

132. Ed Silverman, *State Medicaid Programs Continue to Restrict Access to Hepatitis C Drugs*, STAT (Nov. 14, 2016), <https://www.statnews.com/pharmalot/2016/11/14/medicaid-hepatitis-gilead> [<https://perma.cc/XBS7-QZQ6>].

133. Konnoth, *supra* note 127, at 1352.

134. See generally MICHAEL WALZER, SPHERES OF JUSTICE: DEFENSE OF PLURALISM AND EQUALITY (1983) (offering a theory of justice based upon various spheres of justice).

doctor and patient: Doctors might “becom[e] a skill for their consumer patient.”¹³⁵ As studies have shown, in medical contexts, patients behave differently than in consumer contexts. They defer to doctors, and assume that the doctor shares their goals, and has expertise: “[A]n individual undergoing medical care is often not fully capable of making the best medical decisions and is dependent on those around her.”¹³⁶ Maintaining a separate sphere in which medical action takes place, I have argued, is therefore essential to serve important ethical goals.

In the case of the FDA, the courts similarly seem to distinguish between health related and non-health related considerations. Take *POM Wonderful v. Coca-Cola*.¹³⁷ That case concerned whether a company could bring a mislabeling claim under the Lanham Act against a competitor to protect its commercial interests, or whether such a mislabeling claim when it applied to a product regulated under the FDCA was precluded. The Supreme Court concluded that “the Lanham Act and the FDCA . . . each [have their] own scope and purpose.”¹³⁸ Both touch on food and beverage labeling, but the Lanham Act protects commercial interests against unfair competition, while the FDCA protects public health and safety.” Similarly, the district court in *Tummino v. Von Eschenbach* excoriated the FDA for showing “bad faith” and “improper concerns about the morality of adolescent sexual activity.”¹³⁹

Further, the FDA has itself, on numerous occasions, sought to deny consideration of non-health effects—even as it so often takes them into account. In the *Tummino* case, the court recounts how numerous agency staffs noted that apart from the fact that the evidence showed concerns about sexual activity were groundless, considering ethical issues was beyond their mandate.¹⁴⁰ Similarly, in approving the human growth hormone, the advisory committee concluded that “that once demonstrated to be safe and effective, the choice of whether to attempt therapy for, for example, baldness, or mild acne, or even overweight is up to doctors, patients and their families as they weigh the potential benefits of the therapy against the potential risks.”¹⁴¹

135. Craig J. Konnoth, *Transparency Versus Informed Consent: The Patient/Consumer Paradigms*, in *TRANSPARENCY IN HEALTH AND HEALTH CARE* 75, 78 (Barbara Evans et al. eds., Cambridge Univ. Press 2019).

136. *Id.*

137. *POM Wonderful LLC v. Coca-Cola Co.*, 134 S. Ct. 2228, 2231 (2014).

138. *Id.*

139. *Tummino v. Von Eschenbach*, 427 F. Supp. 2d 212, 233 (2006).

140. *Id.*

141. Matt Lamkin, *Regulating Identity: Medical Regulation as Social Control*, 2016 *BYU L. REV.* 501, 536 (quoting FDA, ENDOCRINOLOGIC AND METABOLIC DRUGS ADVISORY COMMITTEE MEETING (2003)).

Similarly, when it came to animal cloning, the FDA emphatically noted that it could not consider “moral, religious, or ethical issues.”¹⁴²

Despite the weight of this authority, two considerations counsel the broadening of the FDA’s approach, from considering only physiological effects to ethical and political considerations. The first set of considerations concerns the malleability of medical understanding. The second concerns the institutional place of the FDA as a political entity.

First, while it is important to maintain medical practice as a separate sphere of human activity, our understandings of its reach evolve over time. Indeed, ethical concerns, such as those about patient autonomy, and practices which seek to vindicate those concerns, such as informed consent, were historically absent from routine medical practice; today, they have become a bedrock.¹⁴³ The so-called “bioethics revolution,” that today characterizes medical practice and medical research, deeply concerns the FDA, which monitors both research studies, and the outcomes of clinical practice.¹⁴⁴ Considering the ethical results of drug approval is emphatically part of “the way we do things here.”¹⁴⁵

Take one example: In the context of drugs that lead to human enhancement, scholars have argued that the FDA should take into account ethical and normative concerns. Dov Fox, for example, points out that the FDA Advisory Committee ignored the ethical considerations the American Association of Pediatrics raised regarding the human growth hormone, relating to the prejudice shorter individuals might face.¹⁴⁶ As Fox explains, enhancement drugs raise a host of non-health related, but ethical concerns, including “unfairness in competitive activities, inequality of access to positional advantages, perpetuation of social prejudice, threats to individual agency, identity, and authenticity, social conformity and subtle coercion, and negative externalities when such technologies are pursued collectively.”¹⁴⁷

As we gradually reexamine the role of medical entities, we might also engage in policy change that would more firmly ground the FDA’s action. Thus, Fox, along with a range of other ethicists, have therefore urged that the FDA consider the ethical harms these drugs create. Fox suggests a separate “administrative process” within the FDA.¹⁴⁸ Others have urged the creation of

142. FDA’s *Response to Public Comment on the Animal Cloning Risk Assessment, Risk Management Plan, and Guidance for Industry*, FDA, www.fda.gov/AnimalVeterinary/SafetyHealth/AnimalCloning/ucm055491.htm [<https://perma.cc/R3CV-TZZU>].

143. See generally ROBERT BAKER, *BEFORE BIOETHICS: A HISTORY OF AMERICAN MEDICAL ETHICS FROM THE COLONIAL PERIOD TO THE BIOETHICS REVOLUTION* (2013) (providing a historical overview of ethical developments in the medical field).

144. See, e.g., FDA’s *Sentinel Initiative*, FDA, <https://www.fda.gov/safety/fdas-sentinel-initiative> [<https://perma.cc/2B4C-5FCH>] (last updated May 21, 2018).

145. Konnoth, *supra* note 127, at 1352.

146. Fox, *supra* note 14, at 1183–84.

147. *Id.* at 1195.

148. *Id.* at 1194–97.

new regulatory entities, such as an “ethics review board”—effectively an additional advisory committee to “provide comparable advice on the ethical and social dimensions of the agency’s actions.”¹⁴⁹

Fox and others are taking already-existing widely shared understandings about how one practices medicine and research—claims of autonomy, authenticity, equity, and justice—and showing how those existing norms apply in the FDA context. However, these norms, as I noted above, developed through transformation in the ethics of medical practice and research. Reformers today seek to further these transformations, expanding our understandings of the proper scope of medical attention.

Take, for example, a recent article by law professor Zack Buck.¹⁵⁰ Buck explores the concept of “financial toxicity” that has appeared in the medical literature.¹⁵¹ This concept refers to the phenomenon where individuals who suffer financial burdens in the course of receiving care have more health problems and higher mortality rates than those who do not.¹⁵² Buck admits the conceptual barrier between the quality of care and the cost of care may have been meant to serve the purpose of ensuring that individuals received care without rationing.¹⁵³ But now, he argues “[t]o completely separate ‘cost’ from ‘quality’ seems not only unhelpful, but harmful to the actual quality of care that is being delivered by the provider.”¹⁵⁴ He advocates permitting medical malpractice suits against providers who do not integrate ideas of financial toxicity into their healthcare paradigm.

Buck seeks to break down the traditional barrier between medical care and cost of care. Indeed, the term “financial *toxicity*,” which appears to have been coined by doctors, is aimed at collapsing the conceptual difference. Financial hardship is collapsed into physiological harm.¹⁵⁵ Interestingly, Buck

149. Gary Marchant et al., *Integrating Social and Ethical Concerns into Regulatory Decision-Making for Emerging Technologies*, 11 MINN. J.L. SCI. & TECH. 345, 360 (2010); see also Ellen M. McGee, *Should There Be a Law? Brain Chips: Ethical and Policy Issues*, 24 T.M. COOLEY L. REV. 81, 92 (2007) (noting that the FDA “is inadequate to consider the social and policy questions raised by . . . enhancement devices,” thus requiring new regulatory mechanisms). Notably, internal entities have commented on this issue even before most academics. See Secretary’s Advisory Committee on Genetic Testing, 65 Fed. Reg. 21,094, 21,095 (Apr. 19, 2000) (finding that the FDA fails to review “the ethical and social implications” of genetic tests and arguing that “[t]he Secretary should consider the development of a mechanism to ensure the identification, and appropriate review, of tests that raise major social and ethical concerns”).

150. See generally Isaac D. Buck, *The Cost of High Prices: Embedding an Ethic of Expense into the Standard of Care*, 58 B.C. L. REV. 101 (2017).

151. *Id.* at 103.

152. *Id.* at 108.

153. *Id.* at 141.

154. *Id.*

155. *Id.* at 108 (noting that “patients who are saddled with exorbitant medical costs actually experience *worse* health outcomes as a result of the cost of their care—suggest[ing] that treating a patient with an expensive pharmaceutical drug is not just bad for Medicare or the patient’s financial wellbeing, but it may be bad for the patient’s health as well”).

notes in passing: “If one can make the argument that choosing expensive drugs subjects the patient to untenable side effects (based upon the effect of the care on one’s financial wellbeing, and therefore, one’s physical health), then doctors have a duty to the patient” to avoid them where possible.¹⁵⁶ I would argue that the drug regulatory apparatus has a similar role.

Buck’s argument is of a similar cloth to a broader literature on what’s called “social determinants of health.” These are “the structural determinants and conditions in which people are born, grow, live, work and age.” They include socioeconomic status, race, education, environment, employment, social support networks, access to health care, and the like.¹⁵⁷ On that account, drugs’ effects on a multitude of contexts affect individuals’ health, and (indirectly, one might say) their bodily functioning. Thus, scholars have, in some contexts, called for “health impact assessments,” that, much like environmental impact tools, will calculate the downstream effects of a particular action on health.¹⁵⁸

Similar arguments could be made about concerns regarding the sexual activity of minors and the race-stigma effects of BiDil. Sexual activity might produce a range of health-related effects that the FDA is well-equipped to consider. As the *Tummino* court noted, at multiple stages of the process, FDA staff reviewed data about adolescent usage of Plan B, which demonstrated that there was “neither an increase in risky behaviors nor . . . in appropriate use” among adolescents.¹⁵⁹ Similarly, in the case of BiDil, well-established evidence shows that social stigma and discrimination, results in negative health outcomes—both because of the minority stress caused by stigma in a range of contexts, and a fear of discrimination in accessing healthcare, which deters healthcare uptake.¹⁶⁰ Thus, in both cases, the FDA would have had appropriate health related-reasons to take into account these considerations.

So much for the malleability of medical understandings. However, there is a second reason for the FDA to take into account blatantly political, or

156. *Id.*

157. See Samantha Artiga & Elizabeth Hinton, *Beyond Health Care: The Role of Social Determinants in Promoting Health and Health Equity*, HENRY J. KAISER FAM. FOUND. (May 10, 2018), <http://kff.org/disparities-policy/issue-brief/beyond-health-care-the-role-of-social-determinants-in-promoting-health-and-health-equity> [<https://perma.cc/75KW-QD6R>].

158. Eileen O’Keefe & Alex Scott-Samuel, *Human Rights and Wrongs: Could Health Impact Assessment Help?*, 30 J.L. MED. & ETHICS 734, 735–36 (2002). Information about health impact assessments (“HIAs”) can be found on the World Health Organization website. *Health Impact Assessments*, WORLD HEALTH ORG., <http://www.who.int/hia/en> [<https://perma.cc/U7UQ-3NHB>]; see also R. QUIGLEY ET AL., HEALTH IMPACT ASSESSMENT: INTERNATIONAL BEST PRINCIPLES, 1–3 (2006) (summarizing health impact assessments).

159. *Tummino v. Von Eschenbach*, 427 F. Supp. 2d 212, 220 (E.D.N.Y. 2006).

160. The vast literature on minority stress finds that “stressors such as homophobia are associated with greater physical and mental health problems.” Michael P. Dentato, *The Minority Stress Perspective*, AM. PSYCHOL. ASS’N (Apr. 2012), <https://www.apa.org/pi/aids/resources/exchange/2012/04/minority-stress> [<https://perma.cc/7GE4-HNQ5>]. The literature is too vast to cite here.

purely economic considerations even if there is no plausible case that they are related to the field of health—it is an executive agency. It therefore has shared normative allegiances. As a medical entity, it owes allegiance to the norms of medical practice and research. As a political entity, it is required to follow the prescriptions that apply to those entities as well. As the next Part details, the norms of such administrative agencies suggest that such effects be considered.

V. THE POLICY CASE FOR CONSIDERING 'OTHER' SIDE-EFFECTS

The last Part looked at the ethical strictures that come with each of the kinds of the side-effects this Article alludes to and argues that ethical norms suggest considering them. This Part now turns to the policy, legal, and administrative advisability of considering such side-effects in general. It argues that overall, considering such effects validates policy, transparency, and information gathering values, and that objections are limited. And indeed, in some specific instances, specific objections to considering a particular effect might be offered as part of the systematic, methodical, rational approach to considering these effects that I am advocating.¹⁶¹

A. CONSEQUENTIALISM

Scholarship, case law, and regulatory approaches in the administrative law field overwhelmingly advocate for consequentialist reasoning, in particular, cost-benefit analysis, as a necessary guide to agency decisionmaking.¹⁶² Such consequentialist reasoning undergirds much administrative decisionmaking. Embedded within this logic is the need to consider ancillary harms and benefits—whether indirect, third-party, or even non-health.

Even as agencies seek to produce certain desired effects through their regulation, the regulation's benefits are offset by unintended, so-called ancillary, effects which produce costs. But “[t]unnel vision’ within agencies prevents them from considering ancillary effects altogether—both positive and negative.”¹⁶³

As scholars and judges explain, the logic of consequentialism and, relatedly, CBA, means that an intervention whose ancillary costs are heavy

161. For example, in some cases, the FDA might note that it would step on the toes of other agencies and refuse to regulate a certain effect. Such conflict has occurred in the past. *See, e.g., Memorandum of Understanding Between the Federal Trade Commission and the Food and Drug Administration*, FDA, <https://www.fda.gov/about-fda/domestic-mous/mou-225-71-8003> [<https://perma.cc/EC86-2MZ6>]. Preventing conflict with another agency's jurisdiction, however, would be a rational basis to refuse to consider any of the effects I outline here. My concern is that the rationale be systematic and comprehensible.

162. *See generally* RICHARD L. REVESZ & MICHAEL A. LIVERMORE, *RETAKING RATIONALITY: HOW COST-BENEFIT ANALYSIS CAN BETTER PROTECT THE ENVIRONMENT AND OUR HEALTH* (2008) (recommending cost benefit analysis).

163. Rascoff & Revesz, *supra* note 117, at 1767.

enough should not be made even if it achieves the desired goal.¹⁶⁴ As the OMB has instructed in its Circular A-4 that lays out the optimum approach to CBA:

Your analysis should look beyond the direct benefits and direct costs of your rulemaking and consider any important ancillary benefits and countervailing risks. An ancillary benefit is a favorable impact of the rule that is typically unrelated or secondary to the statutory purpose of the rulemaking . . . while a countervailing risk is an adverse economic, health, safety, or environmental consequence that occurs due to a rule and is not already accounted for in the direct cost of the rule.¹⁶⁵

The FDA often escapes criticism in this literature—in some ways it is the original and most dedicated assessor of such ancillary costs because of its consideration of drug side-effects.¹⁶⁶ Indeed, Samuel Rascoff and Ricky Revesz, in their important article on ancillary effects, explicitly use the term “side effects” to refer to ancillary costs—unconsciously, perhaps, evoking the term so common to FDA assessment.¹⁶⁷ Yet, it would appear that the FDA’s approach isn’t perfect. Under the utilitarian rationale of CBA, there is no justification for discounting indirect, third-party, or non-health harms.

Indeed, although the literature generally does not attempt categorization of ancillary risk, the fact is that consideration of indirect, third-party, or non-field specific harms are very much part of regular CBA analysis. One prominent example is that of “health-health” risk.¹⁶⁸ When agencies implement regulations seeking to improve health, they often impose costs. Imposing costs might reduce wealth. And according to many scholars, reducing wealth can reduce health because wealth and health are inter-reliant. Indeed, one scholar argues that \$7.25 million in regulatory costs in 1980 dollars may cause one statistical fatality, a figure that appears in various judicial opinions.¹⁶⁹

Wealth’s effects on health are at best indirect and often of a third-party nature. For example, Judge Williams of the D.C. Circuit noted in an important

164. Rascoff & Revesz canvas the literature in some detail. *See id.* at 1781–89.

165. Letter from the Office of Mgmt. & Budget to the Heads of Exec. Agencies & Establishments, Circular A-4: Regulatory Analysis 26 (Sep. 17, 2003), <https://www.whitehouse.gov/sites/whitehouse.gov/files/omb/circulars/A4/a-4.pdf> [<https://perma.cc/UP2T-BRAK>].

166. *Id.* With the exception of Rascoff & Revesz, who argue that the FDA does not consider the ancillary benefits of drugs as well as unintended costs. Rascoff & Revesz, *supra* note 117, at 1803.

167. Rascoff & Revesz, *supra* note 117, at 1803.

168. Cass R. Sunstein, *Health-Health Tradeoffs*, 63 U. CHI. L. REV. 1533, 1533–38 (1996). As Rascoff & Revesz explain, these are situations where “the chains of events mediating between regulatory intervention and ancillary harm take a distinctive form—namely a reduction in overall social wealth, which is thought to lead to a reduction in overall social health. Proponents of this methodology begin with the premise that wealthier people and societies are also healthier.” In other words, these are indirect effects. Rascoff & Revesz, *supra* note 117, at 1778.

169. Ralph L. Keeney, *Mortality Risks Induced by Economic Expenditures*, 10 RISK ANALYSIS 147, 154–55 (1990).

opinion that workplace safety regulation can cause “some combination of reduced value of firms, higher product prices, fewer jobs in the regulated industry, and lower cash wages.”¹⁷⁰ This, in turn, he noted, citing the \$7.25 million figure, could cause a loss of life.¹⁷¹ Thus, regulation protecting workers in a certain context indirectly harms third parties in the regulated industry.

This kind of reasoning appears in prominent case law and in regulatory contexts. Other important jurists have made similar references as Judge Williams, often explicitly citing the \$7.25 million figure. Justice Breyer does so in his book on risk regulation and in an important administrative law opinion,¹⁷² as do Judges Easterbrook,¹⁷³ and Posner.¹⁷⁴

Perhaps the “most well-known” example in the regulatory context is OIRA’s decision to stop the review of over 600 workplace contaminants in 1992.¹⁷⁵ As its letter to the agency announcing its decision explained, citing Judge Williams’s then recently issued opinion, “[i]f government regulations force firms out of business or into overseas production, employment of American workers will be reduced, making workers less healthy by reducing their incomes.”¹⁷⁶ However, as I discuss further below, in this case, the agency’s chain of causal connections went too far; Congress faulted the agency’s approach, and the review proceeded.

Consideration of indirect and third-party effects appears even when there is no relationship between wealth and health to be drawn. In *Corrosion Proof Fittings v. EPA*, the Fifth Circuit struck down an EPA rule that sought to reduce asbestos exposure.¹⁷⁷ The court reasoned that the EPA failed to take into account the fact that the likely substitutes for asbestos would themselves be carcinogenic, producing or increasing the same risk it sought to extinguish: “Eager to douse the dangers of asbestos, the agency inadvertently actually may increase the risk of injury Americans face. The EPA’s explicit failure to

170. *UAW v. Occupational Safety & Health Admin.*, 938 F.2d 1310, 1326 (D.C. Cir. 1991) (Williams, J., concurring).

171. *Id.*

172. *See Whitman v. Am. Trucking Ass’ns*, 531 U.S. 457, 490–96 (2001) (Breyer, J., concurring in part and concurring in the judgment); STEPHEN BREYER, *BREAKING THE VICIOUS CIRCLE: TOWARD EFFECTIVE RISK REGULATION* 14 (1993).

173. *See UAW v. Johnson Controls, Inc.*, 886 F.2d 871, 918 (7th Cir. 1989) (en banc) (Easterbrook, J., dissenting) (arguing that because “[t]he net effect of lower income and less medical care could be a reduction in infants’ prospects,” infants might face more risk if women were prevented from accessing jobs in which they faced lead exposure, than if they were allowed to work those jobs), *rev’d*, 499 U.S. 187 (1991).

174. *See Am. Dental Ass’n v. Martin*, 984 F.2d 823, 826 (7th Cir. 1993) (arguing that because OSHA failed to take into account the increased costs to consumers from workplace health precautions to prevent AIDS transmissions, it overestimated how many lives were saved by the regulation).

175. *See Rascoff & Revesz*, *supra* note 117, at 1786–87.

176. 138 CONG. REC. S3809 (daily ed. Mar. 18, 1992) (statement of Sen. Glenn).

177. *Corrosion Proof Fittings v. EPA*, 947 F.2d 1201, 1229–30 (5th Cir. 1991).

consider the toxicity of likely substitutes thus deprives its order of a reasonable basis.”¹⁷⁸

Similarly, in *Competitive Enterprise Institute v. National Highway Traffic Safety Administration*, plaintiffs challenged a fuel standards regulation.¹⁷⁹ Plaintiffs argued that the standards would increase the price of larger, safer cars. This, in turn, meant that more consumers would drive their older, less safe cars, or buy smaller, less safe cars.¹⁸⁰ “By making it harder for consumers to buy large cars, the 27.5 mpg standard will increase traffic fatalities if, as a general matter, small cars are less safe than big ones. They are, as [the agency] itself acknowledges.”¹⁸¹

Notably, in making its calculation, the court mandated that the agency go beyond the specific subject area delineated by the statute. The regulation was imposed pursuant to a statute which aimed at achieving “the maximum feasible average fuel economy level[,]’ . . . tak[ing] into account . . . technological feasibility; economic practicability; [the] effect of other Federal motor vehicle standards on fuel economy; and the need of the nation to conserve energy.”¹⁸² Even though “safety” is not a listed consideration, the agency incorporated it as part of its feasibility analysis in most situations, and the court’s invalidation of the rule depended on safety considerations.

OMB Circular A-4 similarly adopts indirect third-party effects as examples of ancillary benefits and costs. An example of an ancillary benefit, it notes, is “reduced refinery emissions due to more stringent fuel economy standards for light trucks”—assuming that such fuel standards will, because of market effects, cause a lower demand for petroleum products.¹⁸³ Similarly, its example of an ancillary cost is the same as the *CEI* case—“adverse safety impacts from more stringent fuel-economy standards for light trucks.”¹⁸⁴

The consequentialist logic of agency review and CBA therefore supports consideration of indirect, third-party, non-field specific considerations. It is

178. *Id.* at 1221.

179. *Competitive Enter. Inst. v. Nat’l Highway Traffic Safety Admin. (CEI II)*, 956 F.2d 321, 322–23 (D.C. Cir. 1992).

180. See Robert W. Crandall, *Policy Watch: Corporate Average Fuel Economy Standards*, 6 J. ECON. PERSP. 171, 178 (1992) (explaining how stringent CAFE standards can lead to decreased automobile safety); Robert W. Crandall & John D. Graham, *The Effect of Fuel Economy Standards on Automobile Safety*, 32 J.L. & ECON. 97, 101–15 (1989) (finding that NHTSA’s CAFE standard kills thousands of people per year). Judge Williams’s opinion cites the study by Crandall and Graham. See *CEI II*, 956 F.2d at 327.

181. *CEI II*, 956 F.2d at 326.

182. *Competitive Enter. Inst. v. Nat’l Highway Traffic Safety Admin. (CEI I)*, 901 F.2d 107, 114 (1990) (quoting 15 U.S.C. § 2002(a)(4), (e) (1988) (listing the factors) (repealed 1994)); 15 U.S.C. § 2002(a)(4) (granting Secretary of Transportation discretion to amend CAFE standard); 49 C.F.R. § 1.50(f) (2009) (delegating authority to NHTSA).

183. Office of Mgmt. & Budget, *supra* note 165, at 26.

184. *Id.*

somewhat ironic that the agency which has made the most consistent efforts to consider ancillary costs fails to do so in a way that embraces it fully.

B. ACCOUNTABILITY AND LEGITIMACY

The debates over BiDil and reproductive drugs show that agencies will sometimes take into account concerns that are never explicitly discussed in the decisionmaking process. This approach presents numerous concerns.¹⁸⁵

Scholars and judges alike openly acknowledge the influence of politics in the administrative system. As *Chevron v. NRDC*, among the most cited administrative law cases,¹⁸⁶ notes: “an agency to which Congress has delegated policy-making responsibilities may, within the limits of that delegation, properly rely upon the incumbent administration’s views of wise policy to inform its judgments.”¹⁸⁷ Indeed, then-Professor Elena Kagan argued that it was desirable for political concerns to be taken into account—what’s the point of a democracy, she asks, if elections do not change the outcomes of agency practice.¹⁸⁸ If Bush’s policies on reproductive issues helped get him elected, then surely, that should mean something for FDA practice.¹⁸⁹ But even if one does not agree with Kagan,¹⁹⁰ the fact remains that judges and scholars alike recognize that political forces often influence agency decisionmaking.

As administrative scholar Kathryn Watts explains, early twentieth-century administrative scholarship saw agencies as comprised of experts that made decisions based purely on science.¹⁹¹ By the 1980s, this and other models had given way to a “political control model.”¹⁹² Most scholars, including Kagan, placed the locus of political control with the President, pointing to the creation of entities like the Office of Management and Budget that solidified presidential oversight of administrative processes.¹⁹³ Other scholars, however, emphasize the ways in which Congress uses formal and informal means to

185. Michael A. Livermore & Richard L. Revesz, *Rethinking Health-Based Environmental Standards*, 89 N.Y.U. L. REV. 1184, 1186–87 (2014).

186. Chris Walker, *Most Cited Supreme Court Administrative Law Decisions*, 36 YALE J. ON REG.: NOTICE & COMMENT (Oct. 9, 2014), <http://yalejreg.com/nc/most-cited-supreme-court-administrative-law-decisions-by-chris-walker> [<https://perma.cc/C9HR-gTVC>].

187. *Chevron v. Nat. Res. Def. Council, Inc.*, 467 U.S. 837, 865 (1984).

188. Elena Kagan, *Presidential Administration*, 114 HARV. L. REV. 2245, 2378 (2001).

189. *See id.*

190. Lars Noah, for example, does not think the FDA should take into account these considerations. *See* Noah, *supra* note 80, at 590–94. Another argument is that giving the FDA the ability to consider extraneous considerations will allow it to look over the crowd and pick out its friends before coming to a decision. But the evidence above suggests that the FDA does it anyway—without disclosing who those friends are.

191. *See* Kathryn A. Watts, *Proposing a Place for Politics in Arbitrary and Capricious Review*, 119 YALE L.J. 2, 33 (2009).

192. *Id.* at 35.

193. Kagan, *supra* note 188, at 2247–48.

guide agency decisionmaking, including hearings, funding decisions, investigations, and informal contacts.¹⁹⁴

Despite this general understanding, agency decisionmaking records are generally devoid of such information. In the FDA context, this means that the agency's documented advisory committee and other processes explicitly consider only certain data, while sidestepping the actual animating force behind its decision. Watts lays out numerous such examples, some pertaining to the FDA. For example, when the FDA sought to regulate teen smoking in the 1990s, President Clinton intervened heavily in the rulemaking—even announcing the final rule in a Rose Garden ceremony. But the FDA's regulatory material such as its statement of basis and purpose squarely relied on statutory citations and expert data. Presidential policy was eclipsed.¹⁹⁵ Decisions regarding HIV drugs, among others, were similarly politically influenced.¹⁹⁶

The attempt of both the Bush and the Obama administrations to stymie OTC approval of Plan B, however, presents a more recent example of such behavior. As a short-term issue, it prevents us from holding the FDA accountable for political decisions. As a longer-term issue, it saps the morale within the agency, and the legitimacy of the agency's scientific reasoning itself.

First, consider accountability concerns. In the Plan B context, political reasoning permeated the process. The Bush administration had gone out of the usual process to appoint individuals “active in the Right to Life antiabortion world” to the advisory committee, and sought to pacify “constituents who would be very unhappy with . . . an over-the-counter Plan B.”¹⁹⁷ The administration sought to send a “message that we were taking adolescents and reproductive issues seriously.”¹⁹⁸ Similarly, President Obama publicly endorsed Sebelius's decision—which the court suggested “was an election-year decision that ‘many public health experts saw as a politically motivated effort to avoid riling religious groups and others opposed to making birth control available to girls.’”¹⁹⁹

Frustratingly, instead of acknowledging these concerns openly, the FDA hid behind science. During the Bush administration, senior FDA personnel repeatedly claimed that non-approval of OTC status was based on “a lack of

194. Watts, *supra* note 191, at 36–37.

195. *Id.* at 23–24.

196. *See generally* DAVID FRANCE, HOW TO SURVIVE A PLAGUE: THE STORY OF HOW ACTIVISTS AND SCIENTISTS TAMED AIDS (2016) (highlighting the spread of AIDS in the US, the public response to the disease and the politics involved with combating the disease).

197. *Tummino v. Torti*, 603 F. Supp. 2d 519, 528–29 (E.D.N.Y. 2009).

198. *Id.* at 529 (citation omitted).

199. *Tummino v. Hamburg*, 936 F. Supp. 2d 162, 170 (E.D.N.Y. 2013). As some academics pithily put it, “Plan B is more dangerous to politicians than to adolescent girls.” Alastair J.J. Wood et al., *The Politics of Emergency Contraception*, 366 NEW ENG. J. MED. 101, 102 (2012).

adequate data to support appropriate use of Plan B by adolescents under 16” despite receiving evidence from their staff on numerous occasions showing that the risk was minimal.²⁰⁰ In its 2004 refusal, the administration therefore cited an “inadequate sampling of younger age groups.”²⁰¹ Similarly, under the Obama administration, even though the FDA Commissioner sought to approve the drug, the Secretary of HHS, Kathleen Sebelius took the extraordinary step of overruling the Commissioner’s determination because, she claimed, “the *data* submitted for this product do not establish that prescription dispensing requirements should be eliminated for all ages.”²⁰² The district court took apart Sebelius’s reasoning sentence by sentence, in a harshly worded opinion.²⁰³ Similarly, “the FDA . . . pursued a litigation strategy dependent on the assertion of the deliberative process privilege to prevent plaintiffs from obtaining conclusive evidence as to the merits of its claim.”²⁰⁴

Now, it may be important to us as a society to express the “message that we were taking adolescents and reproductive issues seriously.”²⁰⁵ But that is a debate that the FDA should have had openly—as many members of Congress were happy to.²⁰⁶ But instead, because the reasons offered were scientific, there was no way to actually have the debate. As one FDA staff member noted—if data on sexual activity was the problem, and “if this is not enough data upon which to base a decision, it is unclear what could constitute enough data or even if that is a[n] obtainable goal.”²⁰⁷

This approach prevents us from holding agencies—and the courts that review them—accountable for their decisions. As Kathryn Watts explains, avoiding a discussion of non-physiological, moral considerations “creates a type of monitoring gap: an agency’s scientific and technocratic reasoning can be closely monitored, whereas political influences directed toward agencies by Congress or the President will not be publicly disclosed and thus will not be subject to the same type of monitoring and accountability.”²⁰⁸ We are

200. Even before the advisory committee meeting in 2003, when the application was first filed, staff proffered evidence that there would be no increased sexual activity. *Torti*, 603 F. Supp. 2d at 530. After the meeting, staff provided such evidence on numerous occasions over the course of 2004. *Id.* at 531–32.

201. *Tummino v. Von Eschenbach*, 427 F. Supp. 2d 212, 223 (E.D.N.Y. 2006).

202. *Hamburg*, 936 F. Supp. 2d at 167 (emphasis added).

203. *Id.* at 167–68.

204. *Torti*, 603 F. Supp. 2d at 548.

205. *Id.* at 529 (citation omitted).

206. Senators Hillary Clinton and Patty Murray put a hold on the confirmation of an FDA Commissioner till they received assurances that the OTC switch would be approved; senators vowed to block the confirmation of the next Commissioner for similar reasons. *Id.* at 534. As a result of all of this, numerous legislators successfully sought a GAO report that reported that the FDA’s behavior was highly unusual. *Id.* at 537.

207. *Tummino v. Von Eschenbach*, 427 F. Supp. 2d 212, 221 (E.D.N.Y. 2006).

208. Watts, *supra* note 191, at 43.

unable to seek accountability from political actors for their behavior in such contexts.²⁰⁹ Further, courts that review these agencies can themselves hide their policy preferences behind the cloak of technocratic expertise like the agency.²¹⁰ If the agency explicitly embraces policy, it is harder for a court itself to engage in such dissembling.

This kind of behavior harms agencies in long-term ways as well. It saps the morale of agency actors. It is one thing to be told that a particular decision is being made based on policy and is above your paygrade.²¹¹ It is quite another to have one's bosses make claims, purportedly based on science, which flagrantly discount the work of, and data collected by, FDA staff. The staff was asked to complete their review even though they were informed that the decision had already been made.²¹² Their work becomes "merely window dressing."²¹³ This caused "dismay"²¹⁴ among the staff, prompted high profile resignations and sapped morale.

Further, the scientific expertise of the agency itself becomes politicized. Allowing "agencies to disclose political factors could help to take some of the political pressure off of science, creating a more effective separation between science and politics."²¹⁵ But politicizing science to support policy conclusions that the science does not itself point to sullies the value of science. As scholars at a National Academies of Science Workshop noted:

Politicians bring science and scientists into the policy arena in an effort to say "the science is on my side." However, . . . leverage[ing] . . . the public's historical trust in scientists, to move political agendas forward . . . [could mean that the] public, which generally has an unfavorable view of politicians, can extend its negative feelings toward science²¹⁶

209. If democratic accountability means anything, administrative judgments, whether based on values or something else, require explicit and open consideration. As Livermore and Revesz note in CBA, "[t]he unacknowledged consideration of a factor . . . has obvious negative consequences for . . . transparency [and] accountability [Reason-giving, they note,] is . . . 'central to U.S. administrative law and practice'" Michael A. Livermore & Richard L. Revesz, *Rethinking Health-Based Environmental Standards*, 89 N.Y.U. L. REV. 1184, 1233 (2014). Theories of agency legitimacy, accountability (to Congress, the judiciary, and even internally to other administrative entities), and deliberative democracy, promote transparency in government reasoning. *Id.*

210. Watts, *supra* note 191, at 78.

211. As former Deputy Solicitor General under then-Attorney General Kamala Harris, who, as an elected official, had a mandate from the people, this was an experience the author regularly encountered.

212. *Tummino v. Torti*, 603 F. Supp. 2d 519, 530 (E.D.N.Y. 2009).

213. *Tummino v. Von Eschenbach*, 427 F. Supp. 2d, 212, 222 (E.D.N.Y. 2006).

214. *Id.*

215. Watts, *supra* note 191, at 40.

216. NATIONAL ACADEMIES OF SCIENCES, TRUST AND CONFIDENCE AT THE INTERFACES OF THE LIFE SCIENCES AND SOCIETY: DOES THE PUBLIC TRUST SCIENCE? 22 (2015).

There are circumstances in which taking non-health related concerns into account would be problematic. First, a statute might restrict the FDA's ability to take into account non-health considerations in certain circumstances. As I argue below, when it comes to whether to approve a drug, the FDA's discretion is more limited. However, it has more discretion when it comes to putting together risk management strategies. Second, Watts argues that political and policy influences must be "openly and transparently disclosed" to promote accountability.²¹⁷

Third, decisions must be supported by some kind of policy position rather than simple political expediency. Take one example: The Bush administration, as a policy matter, sought to discourage contraceptive access, and promote abstinence. It ran, and won, two elections on this platform.²¹⁸ Accordingly, it would be rational for its agencies to consistently support these policies. On the flipside, the Obama administration took a diametrically distinct approach to contraceptive access. Its decision, which undermined its policy positions, was based on crass election year calculations, and is harder to justify (even though, on the whole, my policy preferences align far more with Obama than Bush). Other unacceptable examples might include making decisions solely to satisfy political donors, or simply for partisan reasons. While agencies could "spin[] . . . raw political decisions as . . . policy choices," the FDA would still be disclosing most of its political influences, permitting more accountability than there is today.²¹⁹

C. INFORMATION

Where there is no open debate, there is also a limited likelihood that the agency has fully investigated and weighed the evidence. This means that the agency will sometimes act based on intuitions rather than on full information where evidence can be adduced and weighed.

Cass Sunstein argues that reason-giving can improve the quality of agency decisionmaking directly by forcing agencies to examine issues in which they have limited expertise.²²⁰ The examples I have offered provide strong support for his claim.

Take the example of Plan B. FDA decisionmakers, as I note above, feared what is effectively risk-compensation behavior. They worried that teens would engage in more frequent intercourse which presents both public health, and

217. Watts, *supra* note 191, at 8.

218. Cynthia Dailard, *New Bush Administration Policy Promotes Abstinence Until Marriage Among People in Their 20s*, 9 GUTTMACHER POL'Y REV. 23, 23 (2006).

219. Watts, *supra* note 191, at 56.

220. See, e.g., Cass R. Sunstein, *Cognition and Cost-Benefit Analysis*, 29 J. LEGAL STUD. 1059, 1091 (2000) (discussing these arguments in favor of reason-giving).

for some, moral, concerns.²²¹ Evidence existed to refute those claims.²²² But there was little room in the FDA decisionmaking process to evaluate and rebut those concerns on the record.

The BiDil approval presented similar concerns. The FDA could have chosen to approve BiDil, but could have encouraged, commissioned, or conducted studies on racialized drugs. Did the availability of such drugs change how doctors saw race in medicine? Did policymakers shift their focus from structural racism to racialized medicine as some feared? The answer, with the benefit of a decade of hindsight, seems no, because BiDil did not have much of an effect on the market. But these are valid questions should similarly focused medications appear again.

Other sociological and value-based concerns abound with drug approval. For example, one study notes that for some women, Viagra increases their sense of gender inequity: “[M]en have even more power than they did before.”²²³ But it is far from clear even from this study whether this is a one-off reaction, or whether this is a broader concern. Should this prove to be a major concern, the FDA might, for example, require that doctors offer counseling to men on gender equity issues before prescribing the drug.

D. OBJECTIONS

1. Time and Cost

The FDA approval process, many argue, is slow and expensive. Slowing down the process even more will cost more money and time. However, I believe that approvers should take into account the cost of the delay—and, as I explain below, I would be satisfied with an approve-and-study approach in most circumstances as a default.²²⁴ Under this approach, there would be no need to pause or delay approvals because of burdens that are non-health related or speculative. But where the harms seem clear, even without much further examination, and higher than the benefits, such as those flowing from high cost drugs across the health system, the FDA should be given the

221. See *supra* notes 86–87.

222. Marc Kaufman, *Morning-After Pill Study Contradicts Claim by Foes: Easy Access Did Not Lead to Riskier Behavior*, WASH. POST, Jan. 5, 2005, at A9.

223. Annie Potts et al., *The Downside of Viagra: Women’s Experiences and Concerns*, 25 SOC. HEALTH & ILLNESS 697, 712 (2003).

224. Sunstein, *supra* note 168, at 1553, breaks down the facts:

First is the cost of delay, understood as the cost of not controlling the regulated risk until more information has been compiled. . . . *Second* is the cost of investigating the ancillary risk *Third* is the benefit of investigating the ancillary risk Under this view, it is of course (and unfortunately) important to know at least something about the possible extent of the ancillary risk and the costs of discovering it.

However, Sunstein concludes—correctly, I think—that such a common-sense assessment is quite possible.

authority to hold up approval, even when the effects go beyond the physiological effects on those receiving the medication.

Further, assuming that society has to avert, compensate, or otherwise absorb the harm, the question is not whether to address the harm, but when and where to address it. While the approval process might have its issues, it might prove to be the proverbial stitch in time that saves downstream sewing.

Discussions about regulation have frequently addressed the choice between *ex post* and *ex ante* regulation. *Ex ante* regulation refers to interventions made before the harm that is sought to be averted; *ex post* to interventions made after. Recently, Brian Galle has challenged defenders of *ex post* regulation, arguing that sometimes *ex ante* regulation served useful purposes.²²⁵

Both *ex ante* and *ex post* approaches can vary in timing. For example, consider *ex ante* prevention of drug injury. Within the FDA process, to prevent an injury resulting from a particular side-effect of a drug, one could intervene before the application is submitted, after the application is approved but just up to the point of the occurrence of the injury: We might provide a blood thinner just before administering medication known to risk blood clots.²²⁶ Tort liability or fines are a set of interventions that take place after the injury.

Galle and his interlocutors present a pros/cons list of *ex ante* and *ex post* regulation that can be generalized along a timeline continuum. The earlier the regulation, the less information one has. It is hard to customize the intervention to the expected for harm or set the deterrent appropriately.²²⁷ But *ex post* regulation can under-deter because of cognitive biases—individuals discount future harms, including punishment and penalties.²²⁸ It might also fail to compensate because of judgment proof defendants or other issues, which Galle refers to liquidity problems.²²⁹

In the drug context, later interventions might also come with a set of unique costs. The first is opportunity cost. The later an intervention that may stop work on a particular drug, the greater the net opportunity loss to society that could have focused its resources elsewhere. Second, and relatedly, there is the problem of deterioration. The longer one waits, the worse a problem

225. See generally Brian Galle, *In Praise of Ex Ante Regulation*, 68 VAND. L. REV. 1715 (2015) (arguing against the developing consensus in favor of *ex post* incentives).

226. *Common Test Shows Blood Clot Risk for Cancer Patients Getting Chemo*, U. ROCHESTER MED. CTR. (Dec. 5, 2005), <https://www.urmc.rochester.edu/news/story/953/common-test-shows-blood-clot-risk-for-cancer-patients-getting-chemo.aspx> [<https://perma.cc/2N2D-NFYF>].

227. As Galle explains, in most cases, each additional unit of negative externality reduction is costlier to achieve. Further, each unit produces fewer benefits to society. Thus, because the “government will lack full information” for this analysis, many commentators argue that “*ex post* regulations will often be preferable to *ex ante* solutions.” Galle, *supra* note 225, at 1725.

228. *Id.* at 1721 (noting that myopic failure to take into account future harms or costs is far too common).

229. *Id.* at 1738–43.

can become. Without intervention, a problem can affect more people, or morph into other problems. Thus, antibiotic resistance might grow if PrEP proves to have risk compensation effects. Similarly, healthcare costs might increase as long as the Hepatitis C drug remains on the market.

Where possible, then, it might be better to intervene earlier on in the process precisely to prevent downstream harms where information can be collected with minimal cost. In other countries, for example, pricing information is demanded before effective approval.²³⁰ Adopting the same approach here might save on increased opportunity costs sunk into drug review and approval.

2. The Kitchen Sink/Overreach Objection

Another concern is that there is no end to the approach I suggest. The agency that is supposed to regulate the toe bone will end up passing judgment on the neck bone; the blacksmith who shoes the horse will decide the fate of the kingdom.²³¹ Having the FDA regulate beyond its bailiwick by taking into account an infinite causal thread will make it master of all, with harmful effects on liberty interests.

Nonetheless, other agencies have been able to cogently take into account follow-on effects without such disastrous results. I suggest nothing that administrators do not already often do, even though the statutory or regulatory language might be slightly different in each case. Thus, the OMB Circular suggests considering “important” ancillary benefits and costs.²³² Congressional approaches to the question have appeared to have adopted a “reasonableness” or “identifiability” standard—agencies should consider any effect that they can identify in a reasonable way.²³³ Academics, similarly, have avoided drawing any bright lines, recognizing the need for flexibility. For example, acknowledging the myriad costs and benefits that agencies could take into account, Sunstein merely cautions that “the agency should avoid double counting; the benefits must be genuinely attributable to the rule in

230. Admittedly, in many of these nations, the review is linked to nationalized medical systems. See Suzanne Elvidge, *UK Government to Tackle High Drug Prices*, PHARM.J. (Sept. 20, 2016), <https://www.pharmaceutical-journal.com/news-and-analysis/news/uk-government-to-tackle-high-drug-prices/20201736.article?firstPass=false> [<https://perma.cc/5D78-72VK>].

231. *For Want of a Nail*, ALL NURSERY RHYMES, <https://allnurseryrhymes.com/for-want-of-a-nail> [<https://perma.cc/4KZN-256V>].

232. Office of Mgmt. & Budget, *supra* note 165.

233. For example, the Clean Air Act requires that certain air standards “shall accurately reflect the latest scientific knowledge useful in indicating the kind and extent of all identifiable effects on public health or welfare which may be expected from the presence of such pollutant in the ambient air, in varying quantities.” 42 U.S.C. § 7408(a)(2) (2012). The one outlying bill is the Regulatory Improvement Act of 1999, which defines substitution risk as “a reasonably identifiable significant increased risk to health, safety, or the environment expected to result from a regulatory option; and [that does] not include risks attributable to the effect of an option on the income of individuals.” Regulatory Improvement Act of 1999, S. 746, 106th Cong. § 621(11)(A)–(B).

question, and they must not be counted more than once in the analyses that accompany more than one rule.”²³⁴

Nonetheless, even if we figure out where to draw the line, some argue that expanding the FDA’s reach to include value judgments will harm liberty interests.²³⁵ But to my mind, the liberty interests cut in both directions. The FDA, like other agencies, will regulate based on values. It would be foolhardy to try and “suppress” value-based instincts “out of the administrative process.”²³⁶ It better respects liberty interests to engage with this kind of reasoning openly and frankly. Further, the calibration approach described in the next Part will address some liberty concerns—when it comes to decisions far afield from agency competence, which include those which are intimate to an individual’s personhood, the statutory structure suggests (and the Constitution probably mandates) that the reach of agency regulation cannot place an undue burden on the individual.

To be sure, sometimes an agency can go too far. OIRA’s decision to suspend the review of workplace safety regulation based on decreased incomes was done without any notice or analysis. It had failed to engage in the kind of evidence determination that some felt was necessary. As Senator Ted Kennedy argued, all it had relied on was “a far-out, off-the-wall, right-wing theory . . . that if employers spend less money on health and safety, they will pay higher wages to employees or charge lower prices for their goods.”²³⁷ Rather than provide further analysis, however, OIRA simply backed down and let the regulatory review proceed. Had context specific evidence developed through a deliberative decisionmaking process been adduced, however, the reaction and outcome may have been quite different.

3. Expertise

The next objection is that the FDA lacks the expertise to carry out the tasks I suggest.²³⁸ However, the statute allows the FDA to obtain expertise as required, a feature it demonstrates regularly in the antibiotic resistance context.²³⁹ The FDA works collaboratively with several agencies and advisory groups in making its decisions. Although creating advisory committees are

234. Cass R. Sunstein, *The Real World of Cost Benefit Analysis: Thirty-Six Questions (and Almost as Many Answers)*, 114 COLUM. L. REV. 167, 190 n.92 (2014); see also Saul, *supra* note 94.

235. Lamkin, *supra* note 141, at 565.

236. David Arkush, *Democracy and Administrative Legitimacy*, 47 WAKE FOREST L. REV. 611, 620 (2012).

237. National Cooperative Research Act Extension, 138 CONG. REC. S3841, S3859 (Sep. 27, 1992) (statement of Sen. Kennedy).

238. Some may argue that another agency should form to carry out this task such as the Centers for Disease Control, or even professional associations. While I do not deny that as a possibility, the genesis for this Article is that the FDA has been engaging in these activities quite frequently—just not methodically.

239. See Zettler et al., *supra* note 15, at 250–51 (noting a role for advisory committees to advise on public health issues).

limited under the Federal Advisory Committee Act of 1972,²⁴⁰ in the FDA context, the Secretary appears to have broad discretion to “(1) establish such technical and scientific review groups as are needed to carry out the functions of the Food and Drug Administration . . . and (2) appoint and pay the members of such groups.”²⁴¹ She also has the ability to contract for expert review and is required to collaborate with other agencies on many issues.²⁴² Although the Secretary is more constrained with respect to whom she can appoint to some committees,²⁴³ with most—especially the ones pertaining to drug application, withdrawal, and advertising—she has great discretion. She therefore can appoint individuals who would be cognizant of harms broader than mere physiological harms, ranging from concerns related to marginalization and health costs.

“For the purpose of providing expert scientific advice . . . regarding . . . the approval for marketing of a drug . . . the Secretary shall establish panels of experts.”²⁴⁴ Similar panels exist for classifying devices, for example, as needing pre-market approval.²⁴⁵ The Secretary has discretion to appoint members with appropriate qualifications, including those “qualified by training and experience to evaluate the safety and effectiveness of the device”²⁴⁶ In some cases, the Commissioner must refer an opioid application to a committee unless she finds, *inter alia*, that such a referral “is not in the interest of protecting and promoting public health.”²⁴⁷ “[The] FDA generally follows an advisory committee’s recommendation, but is not bound to do so.”²⁴⁸

The statute to some extent requires that the FDA rely on advisory committees for continued assessment of the risks that new drugs pose, review that may ultimately lead to withdrawal. “At least biannually, the Secretary shall seek recommendations from the Drug Safety and Risk Management Advisory Committee” on assessing drug safety in the field.²⁴⁹ The Secretary must also act “through” the committee in some cases.²⁵⁰ The Secretary may also convene

240. Federal Advisory Committee Act, Pub. L. No. 92-463, 86 Stat. 770 (1972).

241. 21 U.S.C. §§ 394, 379d-1 (2012).

242. *Id.* § 397(a) (contracts for expert review); *id.* § 355e(b)(4) (enforcement); *id.* § 356(c) (decrease in lifesaving drugs; collaboration with DOJ).

243. However, the manufacturing requirements committee has nine members and is more restrictive. *Id.* § 360j(f)(3).

244. *Id.* § 355(n)(1).

245. *Id.* § 360c(b).

246. *Id.* § 360c(b)(2); 21 C.F.R. § 314.50(c)(1) (2018).

247. Comprehensive Addiction and Recovery Act of 2016, Pub. L. No. 114-198, § 106(a)(1)(B)(i), 130 Stat. 695, 702.

248. *Human Drug Advisory Committees*, FDA, <http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs> [<https://perma.cc/9G5S-QR5B>] (last updated Oct. 5, 2017).

249. Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 355(k)(4)(C).

250. *Id.* § 355-1(f)(5).

meetings to review safety concerns and the risk mitigation strategy involving a drug.²⁵¹

The FDA also takes input from other entities in reviewing communication and advertising. The Advisory Committee on Risk Communication acts to “advise the Commissioner on methods to effectively communicate risks associated with the products regulated by the Food and Drug Administration.”²⁵² The Secretary has latitude to determine who is appointed to the committee. She also has the authority to go beyond the committee.²⁵³ In reviewing “scientific evidence and research on decisionmaking and social and cognitive psychology” the Secretary must “consult with drug manufacturers, clinicians, patients and consumers, experts in health literacy, representatives of racial and ethnic minorities, and experts in women’s and pediatric health.”²⁵⁴ In other words, the Secretary has the authority to ensure that each committee has members that are experts on the effects of these various drugs that extend beyond the physiological effects of drugs.

The FDA should continue working with and soliciting the opinion of state health entities, expand communication with formulary committees of large entities, as well as other stakeholders to determine best practices. It should also take advantage of the consultative benefits available to all agencies.²⁵⁵

4. Federalism

Should states have a role in this process? Most scholars involved in the debates over federalism in the drug regulation process agree that when the FDA has considered the harms of a drug, and decided to take or withhold

251. *Id.* § 355-1(h)(5).

252. *Id.* § 360bbb-6(a)(2).

253. Patient Protection and Affordable Care Act, Pub. L. No. 111-148, § 3507, 124 Stat. 119, 530 (2010).

254. *Id.* Further, outside entities help establish “innovative, collaborative projects in research, education, and outreach for the purpose of fostering medical product innovation, enabling the acceleration of medical product development.” 21 U.S.C. § 360bbb-5.

255. Jonathan Baert Wiener & John D. Graham, *Resolving Risk Tradeoffs*, in *RISK VS. RISK: TRADEOFFS IN PROTECTING HEALTH AND THE ENVIRONMENT* 251 (1995), for example, suggest that OIRA develop greater expertise in these kind of risk assessments. Beyond that, they suggest a “primary care” agency, possibly in the White House, which could then holistically treat a regulatory problem, analyzing risks that that more narrowly focused agencies would miss. The primary care agency would refer specific risks to “specialist” agencies as needed. Alternatively, a complex agency could place oversight of risk into a position entitled “Undersecretary for Risk Management.” *See id.* at 258.

action, states are generally preempted from counteracting the FDA.²⁵⁶ The Supreme Court has also weighed in on the question.²⁵⁷

I seek to engage in these debates only in one particular: Allowing the FDA to take into account other considerations beyond physiological health, some might say, would encroach into areas traditionally under state control. Catherine Sharkey, a prolific commentator in these debates, offers the following hypothetical:

[S]uppose that [Massachusetts] enacted a ban on a painkiller drug not due to health and safety concerns, but instead because it wanted to recognize and encourage its citizens' puritanminded, "buck-up in the face of pain" mentality. In such a case, the purpose behind the federal regulations would be different from the state's motivation for action, and the FDA ostensibly would not have considered the state's (non-health and safety) related purposes when regulating. When federal and state actors regulate for different purposes, such that a federal agency is less likely to have considered a state's purported interests, the case for preemption is weaker.²⁵⁸

Sharkey's point is that if the state considers a purpose that the federal government has not considered, then the state's action may not be preempted. My question is—is it legitimate for the federal government take into account such purposes?

The FDA should only be able to take into account policies which reflect a broad national consensus.²⁵⁹ Even if the harm at issue concerns only a particular state—for example, a localized outbreak of some particular condition—if a national policy exists that determines what the outcome should be, the FDA should follow that policy. National policies exist on a range of subjects, ranging from health and safety (preserving lives and resources is good) to ethical standards on racism.

But where norms are localized, the FDA should refrain; where they are in flux, they should be warier. Thus, to use Sharkey's hypothetical, the FDA should refrain from considering New England puritanism in making decisions. In short, the FDA should only take into account a harm as it does now—where there is consensus. Preemption related concerns will arise but

256. See, e.g., Catherine M. Sharkey, *Federalism in Action: FDA Regulatory Preemption in Pharmaceutical Cases in State Versus Federal Courts*, 15 J.L. & POL'Y 1013, 1013–14 (2007). But see generally Lars Noah, *State Affronts to Federal Primacy in the Licensure of Pharmaceutical Products*, 2016 MICH. ST. L. REV. 1 (explaining the difficulties of the argument); Diana R. H. Winters, *The Benefits of Regulatory Friction in Shaping Policy*, 71 FOOD & DRUG L.J. 228 (2016) (explaining why state regulation has its benefits); Patricia J. Zettler, *Pharmaceutical Federalism*, 92 IND. L.J. 845 (2017) (explaining the benefits of state regulation).

257. See *Wyeth v. Levine*, 555 U.S. 555, 558–59 (2009).

258. Catherine M. Sharkey, *States Versus FDA*, 83 GEO. WASH. L. REV. 1609, 1628 n.85 (2015).

259. To be sure, if the cost of identifying whether there is some consensus is onerous, the FDA could say so, see *supra* Section V.D.1.

the exact rule that should be followed in such cases is beyond the scope of this Article.

VI. REGULATORY CALIBRATION

How should the FDA take into account these kinds of non-traditional effects? A full assessment of that question is beyond the scope of this Article. However, my claim is that given that many of the harms I describe exist on a continuum, the FDA's action should also be calibrated to that continuum. In this Part, I attempt to show merely that the FDA's organic statute often offers the possibility of some kind of rough calibration depending on the harm involved. The action the FDA can take might range in severity, involving among other things, (1) drug approval; (2) advertising review; and (3) post approval surveillance and possible withdrawal, among others. The FDA's action in dealing with these harms, based on the logic of the statute and other criteria, should be calibrated based on the directness of the drug's effect, the scope of the entities affected, and whether there is a core health concern involved. It bears noting that the calibration framework is already familiar to FDA regulation. The statute, for example, requires that REMS "to assure safe use" which might range simply from labeling, to distribution restrictions "shall . . . be commensurate with the specific serious risk."²⁶⁰ My claim is that broader FDA regulation should conform to a similar approach.

A. DESCRIBING REGULATORY CALIBRATION

Calibrated enforcement has received significant attention in administrative scholarship. In their highly cited work, *Responsive Regulation*, Ian Ayres and John Braithwaite place regulatory action on a so called "enforcement pyramid."²⁶¹ The pyramid describes a "range of interventions of ever-increasing intrusiveness (matched by ever-decreasing frequency of use)."²⁶² At the base of the pyramid, we find the least intrusive agency action, that one expects applied to the greatest number of firms—persuasion, where the agency informs the firm of the violation and seeks to coax them into compliance. As one goes up the pyramid, the intrusion escalates to warning letters, civil, then criminal, penalties, license suspension, and license revocation—actions that apply to an ever-decreasing number of regulated entities.²⁶³ Scholars have offered other pyramid-like models. Thus, some scholars argue that the pyramid should be reconceptualized as having more

260. 21 U.S.C. § 355-1(f)(2)(A) (2012).

261. AYRES & BRAITHWAITE, *supra* note 18, at 6.

262. *Id.* at 6.

263. *See id.* at 35.

facets, with other social entities, in addition to the government, placing escalating burdens on firms for non-compliance.²⁶⁴

What might the pyramid look like in the FDA context? The FDA interventions I list in Part II—approval, advertising and labeling, REMS requirements, and post market surveillance, are best understood as ranging in levels of intensity. Three criteria determine the level of intensity: burden, blanket effect, and timing. The FDA's actions affect manufacturers, doctors, patients, indeed, the entire medical system. We might assess the FDA's behavior with respect to all of these entities in order to determine the level of intensity.

The first criterion is severity, measured by the extent of force exercised on the subject of the regulation to achieve the desired effect. Administrative scholars point to a range of severity ranging from nudging to coercion.

Cass Sunstein and Richard Thaler have famously advocated for a “nudge” regime in many contexts, where entities can use techniques to guide individual choices to help them avoid the cognitive biases individuals exhibit in making decisions. The extent to which these techniques impose costs on individuals—and the extent to which they affect decisionmaking—are a matter of degree.²⁶⁵ In some cases, the effect is unavoidable: How one orders food in a cafeteria will affect individuals' dietary choices. Sunstein and Thaler argue that since *some* order has to be chosen anyway, choosing the ordering that produces the best dietary choices is minimally coercive.²⁶⁶

But the coercion lies on a spectrum. For example, one might have voluntary information release, or compelled information release—Sunstein and Thaler point to the FDA's tobacco labeling regulation as an example.²⁶⁷ Default options might involve low-cost, one-click opt-outs—for example, opting out of data privacy protections on websites. Or the costs of opting out might be higher—filling out a form for example, to opt out of health insurance coverage. As Pierre Schlag puts it, “a nudge” can become “a shove.”²⁶⁸ Further, “[s]omeone's nudge is someone else's” coercion—“[o]ne suspects, for instance, that those who are blacklisted as a result of compelled-

264. Neil Gunningham & Darren Sinclair, *Integrative Regulation: A Principle-Based Approach to Environmental Policy*, 24 L. & SOC. INQUIRY 853, 855 (1999). Some scholars have also discussed the article in the context of Food & Drug law. See generally Stuart Hogarth et al., *Closing the Gaps—Enhancing the Regulation of Genetic Tests Using Responsive Regulation*, 62 FOOD & DRUG L.J. 831 (2007) (explaining how the current regulatory framework is inadequate). However, in so doing, they essentially replicate Ayres's and Braithwaite's arguments.

265. RICHARD H. THALER & CASS R. SUNSTEIN, *NUDGE: IMPROVING DECISIONS ABOUT HEALTH, WEALTH, AND HAPPINESS* 251 (2009). See generally ROBERT BALDWIN, *NUDGE: THREE DEGREES OF CONCERN* (2015), https://eprints.lse.ac.uk/64049/1/Policy%20Briefing%207_2015.pdf [<https://perma.cc/L76B-6WAV>] (discussing degrees of nudging).

266. THALER & SUNSTEIN, *supra* note 265, at 10.

267. *Id.* at 191.

268. Pierre Schlag, *Nudge, Choice Architecture, and Libertarian Paternalism*, 108 MICH. L. REV. 913, 917 (2010) (reviewing the above cited book by Thaler & Sunstein).

disclosure requirements will view the requirements as coercive, not a nudge at all.”²⁶⁹ But of course, not all shoves are impermissible.

A glance at some of the FDA’s regulatory mechanisms reveals a spectrum of nudges-into-coercion, and we might look at a variety of criteria to determine where on the spectrum we are. With respect to manufacturers, we might assess this criterion by looking at the severity of the penalty the FDA would impose if the manufacturer were to engage in impermissible behavior. The FDA might impose heavy damages or imprisonment if the manufacturer flouted an FDA command, or simply issue an advisory with no further penalty.²⁷⁰

With respect to doctors and patients, whom the FDA cannot penalize, *per se*, severity might be measured in degree of access to the drug. FDA action that bans the drug wholesale or for certain populations is coercion—it physically prevents access. FDA action that allows the drug to be administered but with appropriate advertising or warnings is a form of nudging.

Another criterion involves the reach of the FDA’s action. The FDA might take blanket action, approving the drug for all individuals or requiring blanket advertising. In practice, of course, the FDA engages in some degree of customization at the time of approval, by limiting access based on condition, and sometimes imposing additional conditions that limit drug availability and require certain labeling information.²⁷¹ As a general matter, though, it does not generally penalize off-label use.²⁷²

269. *Id.*

270. The FDA website, for example, recounts a spectrum of possible penalty. *Recalls, Corrections and Removals (Devices)*, FDA, <https://www.fda.gov/medicaldevices/deviceregulationandguidance/postmarketrequirements/recallsandremovals/default.htm> [<https://perma.cc/PA9X-SFWR>]. As the FDA explains, actions might range from “[c]orrection” which “means repair . . . relabeling . . . or inspection (including patient monitoring) of a product *without* its physical removal.” *Id.* “Market withdrawal” can “mean[] a firm’s removal . . . which involves a minor violation that would not be subject to legal action by the FDA.” *Id.* “Recall means a firm’s removal or correction of a marketed product that the FDA considers to be in violation of the laws it administers and against which the agency would initiate legal action.” *Id.* Recalls themselves are subject to spectra. Thus, “[m]edical device recalls are usually conducted voluntarily by the manufacturer.” *Id.* But in serious enough situations, where the manufacturer is not complying, the “FDA may issue a recall order to the manufacturer.” *Id.* Other factors include the “[d]epth of recall. Depending on the product’s degree of hazard and extent of distribution, the recall strategy will specify the level in the distribution chain to which the recall is to extend.” *Id.* Finally, another escalation is “a public warning . . . to alert the public that a product being recalled presents a serious hazard to health. This is reserved for urgent situations where other means for preventing use of the recalled product appear inadequate.” *Id.*

271. Evans, *supra* note 33, at 512.

272. *Understanding Unapproved Use of Approved Drugs “Off Label,”* FDA, <https://www.fda.gov/ForPatients/Other/Offlabel/default.htm> [<https://perma.cc/JHT5-QQZ2>]; see also Legal Status of Approved Labeling for Prescription Drugs; Prescribing for Uses Unapproved by the Food and Drug Administration, 37 Fed. Reg. 16,503, 16,504 (Aug. 15, 1972) (stating that labeling is not intended to impede the physician’s exercise of judgment concerning what is best for the patient or to impose liability for prescribing decisions that are at odds with drug labeling).

One could imagine a range of other customized approaches that reflect different degree of coercion/choice alternation/nudging, some which are not statutorily sanctioned under current law. For example, drugs may be approved on the condition that manufacturers price discriminate. To prevent an entire insurance pool from being harmed, those who cost share more can be asked to pay full price. We might also demand price discrimination based on the patient's income, and whether the insurance program is public or private.

By allowing such discrimination, we might optimize social value. As I explain above, ensuring that only individuals who do not already use condoms get PrEP would be optimal.²⁷³ Similarly, even if BiDil worked better in some races than others, we might want to restrict access to a race-based drug to only those situations where its marginal benefit over the next best alternative is significant. (BiDil's manufacturer never had to prove such a benefit). Such an approach would signal the FDA's reluctance to endorse racialized medicine and would alleviate the harms of the drug's approval. Overall, with medical improvements, precise customization might become possible.²⁷⁴

Finally, the timing of the FDA's intervention also affects how intense its action appears. The withdrawal of a drug is, in some ways, a more severe action than refusing to approve a drug in the first place. Manufacturers and those who worked on drug research and development may experience an endowment effect in knowing that their drug is approved and on the market.²⁷⁵ More importantly, consumers who might be habituated to certain drugs or regimens might find withdrawal to be more burdensome. On the other hand, withdrawing the drug at a later date will ensure that manufacturers have a chance to recoup at least some of their outlays.

B. JUSTIFYING CALIBRATION

In proposing calibration, Ayres and Braithwaite—and other scholars since—offer a set of justifications that differ significantly from the ones I offer here. Their proposal comes from a game theory perspective, focused on the question of compliance. As they explain, while relying solely on persuasion “will be exploited when actors are motivated by economic rationality,” relying “mostly on punishment will undermine the good will of actors . . . [who are] motivated by a sense of responsibility.”²⁷⁶ Further, “[p]unishment is expensive; persuasion is cheap.”²⁷⁷ Thus, they argue, it is more efficient to escalate up the pyramid only when the firm proves itself unwilling to comply

273. See *supra* note 54 and accompanying text.

274. See generally Craig Konnoth, *Health Information Equity*, 165 U. PA. L. REV. 1317 (2017) (highlighting the rise in health information being collected to tailor medical care to specific individuals).

275. Craig Konnoth, *Revoking Rights*, 66 HASTINGS L.J. 1365, 1382 (2015).

276. AYRES & BRAITHWAITE, *supra* note 18, at 19.

277. *Id.*

with more limited interventions. These claims have received expansion, support and criticism. For example, scholars, perhaps most prominently in the tax literature—question the efficacy of the model. Starting low and escalating enforcement often leads to undercompliance, they claim.²⁷⁸

While I too am interested in the question of calibration, it is for very different reasons. I am not interested in its efficacy in inducing compliance. Rather, I am interested in agency competency, legitimacy, and legality. This offers an additional set of arguments to the literature on calibrated regulation.

The competency-based arguments are fairly straightforward. The FDA should stay its hand the more indirect, third-party, and non-health-related a drug's effects are. Given existing disciplinary boundaries, FDA personnel are the most likely to have expertise on issues connected with health and, specifically, physiological effects. Evaluating concerns in other areas might involve intervening on issues they know little about. Accordingly, in such areas, advisories or flagging issues for further study would be more apposite than flat out bans.

Next, even in areas where the FDA has expertise, there is uncertainty. As effects are further removed from the initial cause, the possibility of other intervention increases uncertainty.²⁷⁹ Third-party and society wide effects will mostly (though not always) be intermediated by other factors. Predicting risk compensation is a fraught exercise, mediated by individual perceptions, preferences, and circumstances, that will vary greatly across groups. An approve-and-study approach is likely superior to a ban-and-study approach.

Competency based arguments are connected to legitimacy-based arguments. Even if the FDA had expertise and could make sound predictions, in a world with disciplinary boundaries, any overreach could, as a practical matter, sap its perceived legitimacy. It could also result in inter-agency warfare. Thus, the FDA could engage concerns about race and BiDil with agencies like the Office of Civil Rights in HHS for example. It could also have conceivably intervened on BiDil related advertising to ensure that it is racially sensitive and did not exacerbate stigma. But a straight ban on BiDil purely because of concerns regarding race would have been an extreme step.

Legitimacy arguments, in turn, connect to concerns over legality, both constitutional and statutory. These arguments are more complex. First, constitutional law suggests some degree of calibration is necessary. Even if

278. Leigh Osofsky, *Some Realism About Responsive Tax Administration*, 66 TAX L. REV. 121, 128 (2012).

279. Chief Judge Mikva, without rejecting the approach in principle, hinted at a similar observation in *Competitive Enterprises*: “The majority’s predictions about effects on the behavior of both manufacturers and consumers and the likely safety consequences of these anticipated effects . . . represent musings that the agency considered and reasonably rejected.” *Competitive Enter. Inst. v. Nat’l Highway Traffic Safety Admin.*, 956 F.2d 321, 329 (D.C. Cir. 1992) (Mikva, C.J., dissenting in part); see also Rascoff & Revesz, *supra* note 117, at 1777.

constitutional law does not *require* calibration in this context, constitutional doctrine in analogous contexts suggests that calibration here is the preferred, more legitimate, approach.

In constitutional cases, the concept of calibration is best captured by the “proportionality” principle. As Vicki Jackson recently explains, according to the principle “larger harms imposed by government should be justified by more weighty reasons and that more severe transgressions of the law be more harshly sanctioned than less severe ones.”²⁸⁰ Jackson offers a full defense of the principle in American constitutional law, both as a civil and criminal matter, but a sketch here is appropriate.

In many constitutional contexts, courts have intuitively, albeit not in any systematic way, considered the importance of the state’s goal, the extent of the burden, and ‘fit.’ For example, when certain important—fundamental—rights are infringed, the Court demands strict scrutiny, justified by a compelling state purpose and a narrowly tailored fit. When other, less important rights are infringed, the calibration is taken down a notch, with a relaxed purpose/fit requirement.

The Court’s calibration appears to consider, not just the nature of the right, but the nature of the burden, which in turn appears to track intuitions constituent with the regulatory pyramid. Consider Alan Brownstein’s well-known article defending the development of the undue burden standard in reproductive rights cases. In that context, he argues, the Court looks, not just to the importance of the right, but to the severity of the burden the state imposes. An incidental burden of even important rights receives only rational basis scrutiny. But more substantial—or undue—burdens of those rights receive strict scrutiny.²⁸¹ Thus, as in *Planned Parenthood v. Casey*, a disclosure requirement by doctors triggered very deferential constitutional scrutiny—such disclosure requirements, as a regulatory matter appear quite attenuated.²⁸² But more severe burdens on the abortion right, such as outright bans, receive more searching scrutiny. But as the government’s interest in fetal life increases as the fetus becomes more viable, the more rigorous the burden it can impose on abortion.

Notably, the Court’s approach, and Brownstein’s analysis, does not appear to depend on any analysis that is particular to the abortion context. The Court’s analysis in this context, if not textually unmoored, seem to be based as much on common sense as upon exegesis of precedent and doctrine.

280. Vicki C. Jackson, *Constitutional Law in an Age of Proportionality*, 124 YALE L.J. 3094, 3098 (2015).

281. See generally Alan Brownstein, *How Rights Are Infringed: The Role of Undue Burden Analysis in Constitutional Doctrine*, 45 HASTINGS L.J. 867 (1994) (providing analysis on the undue burden standard for government regulation).

282. See generally *Planned Parenthood of Se. Pa. v. Casey*, 505 U.S. 833 (1992) (holding that the undue burden test rather than a trimester-based approach should be used in the evaluation of restrictions on abortion).

The intuition appears simple—the more extreme the government's action—or to use the administrative argot above, the higher up on the regulatory pyramid it is, the surer and more compelling must be its goals and the fit required.

This intuition appears to have seeped into the administrative context in some form at least. Consider the Fifth Circuit's gloss on the Toxic Substances Control Act, in which it observed that the Act "provides the EPA with a list of alternative actions, but also provides those alternatives in order of how burdensome they are."²⁸³ Much like the FDCA, "[t]he regulations thus provide for EPA regulation ranging from labeling the least toxic chemicals to limiting the total amount of chemicals an industry may use. Total bans head the list as the most burdensome regulatory option."²⁸⁴ In that case, the court found the EPA's challenged action—a total ban on asbestos use—to be problematic because of how drastic it was, an approach "the petitioners characterize[d] as the 'death penalty alternative.'"²⁸⁵ The court held that the EPA was required to use the "least burdensome means" to achieve a particular result.²⁸⁶ It noted, that administrative action lower down the list, such as labeling, might well have achieved the same result that banning asbestos did.²⁸⁷ The overbreadth of the agency action compared to the desired goal appeared to concern the court.

I do not seek to make the case that the constitutional analysis here is systematic or pervasive—as Jackson's analysis shows, it is not. But the intuition that some proportionality is appropriate does appear regularly in constitutional doctrine.

The FDA's actions can affect important interests. Matt Lamkin, indeed, seeks to argue that FDA interference is constitutionally limited: "[w]here medical interventions affect bodily integrity or identity in fundamental ways, the Court has repeatedly recognized that individuals' decisions about these interventions can implicate a 'realm of personal liberty which the government may not enter.'"²⁸⁸ I believe Lamkin's claim is an overstatement. Government intervention affects human behavior and morality in a range of ways. However, the intervention cannot go beyond certain limits—cannot, for example, in the reproductive justice cases, present an "undue burden."²⁸⁹ Calibration helps address these concerns.

Finally, the FDA's organic statute also appears to recommend calibration in some rudimentary form, as I describe in the next Section.

283. *Corrosion Proof Fittings v. EPA*, 947 F.2d 1201, 1215 (5th Cir 1991).

284. *Id.* at 1215–16.

285. *Id.*

286. *Id.* at 1223.

287. *Id.* at 1228.

288. Lamkin, *supra* note 141, at 565 (quoting *Planned Parenthood of Se. Pa. v. Casey*, 505 U.S. 833, 847 (1992)).

289. See Brownstein, *supra* note 281, at 878–79.

C. STATUTORY CALIBRATION

In most of its actions, the FDA can consider safety and public health. Public health requires the FDA to broadly consider health infrastructure related issues, such as supply chain or risk mitigation. This almost certainly brings indirect effects and community or social level harms within its reach. The statute explicitly directs the FDA to consider the psychological or cognitive effects of drugs on individuals and refers to the health of marginalized communities as a public health concern. But while broad, these terms are, of course, limited in scope. The FDA might, for example, consider the taste of a drug if it has health ramifications—for example, if there is evidence that taste affects drug adherence. But it cannot consider the taste of the drug for purely aesthetic reasons. These limits appear relaxed in the advertising context, where the FDA may even more broadly consider “consumer good and well-being.”²⁹⁰

Here I argue that the statute roughly tracks the calibration I lay out above. The statute appears to roughly calibrate the severity of the intervention to the criteria I lay out in Part III. Roughly speaking, when it comes to the most coercive kinds of FDA action—refusal to approve a drug—the FDA can only consider health related issues. While these include public health, safety, and the like, they are more likely to involve first person, direct, physiological harms. And when it comes to withdrawal, which is even more severe than denial, the harm must be “substantial and imminent.” But when providing non-coercive recommendations about advertising, for example, the FDA is able to consider overall consumer “good and well-being.”

I note that I pick these decisionmaking steps as key FDA functions without purporting that they represent an exhaustive list of FDA actions. Other tools in the FDA arsenal, for example, include advisory guidance,²⁹¹ or even conditional approval on the adoption of certain REMS, that might require drugs to be distributed by physicians with special training in certain facilities.²⁹² Although the regulations have rendered the statutory language more specific, as written, the law allows for some leeway.

290. Though given recent First Amendment jurisprudence, more such limits might exist. *See, e.g., Sorrell v. IMS Health*, 564 U.S. 552, 579–80 (2011) (holding that certain state regulation pertaining to drug detailing violated speech rights). I cannot discuss this jurisprudence in detail, confining my comments here to the organic statute.

291. The Food and Drug Administration’s Development, Issuance, and Use of Guidance Documents, 62 Fed. Reg. 8,961, 8,967 (1997).

292. It is questionable whether the FDA had this authority until 2007. *See* Wash. Legal Found. v. Kessler, 880 F. Supp. 26, 34–36 (D.D.C. 1995); Lars Noah, *Administrative Arm-Twisting in the Shadow of Congressional Delegations of Authority*, 1997 WIS. L. REV. 873, 876–82, 886–93, 922–23. However, 2007 statutory amendments have confirmed this authority. *See* Evans, *supra* note 33, at 440; *see also* 21 C.F.R. § 314 (2018).

1. Approval

According to the statute, in applicable part, the Secretary may only refuse to approve a drug if:

[She] finds . . . that . . . the investigations . . . [into the drug] do not include adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions . . . suggested in the proposed labeling thereof; [or] the results of such tests show that such drug is unsafe for use under such conditions . . . [or she] has insufficient information to determine whether such drug is safe for use under such conditions.²⁹³

The statute does not clearly define the term “safe.” Merriam Webster tells us that safe means “free from harm or risk.”²⁹⁴ One could imagine using the drugs described in the previous Part in accordance with the “conditions . . . suggested in the proposed labeling thereof,” and still seeing many of the side-effects I describe. These effects constitute “harms or risks” in common parlance. Thus, while the subject the FDA is asked to consider is the drug’s “safety,” the word, by itself, devoid of further context could implicate a range of effects.

Another clue as to the factors that might go into safety determinations, however, can be gleaned from other provisions of the statute that detail other aspects of the approval process. Consider the provisions concerning risk mitigation strategy. At the time of the application, “[i]f the Secretary . . . determines that a risk evaluation and mitigation strategy is necessary to ensure that the benefits of the drug outweigh the risks of the drug,” approval could be conditioned on the submission of such a strategy.²⁹⁵ The risk mitigation strategy might require medication guides, patient package inserts, or communication plans to the relevant providers. One might fairly conclude that the REMS determination, being part of the approval process, is meant to promote the overall goal of approval, that is, “safety.”

In making a REMS determination, “the Secretary shall consider . . . factors” including “[t]he estimated size of the population likely to use the drug[,] . . . [t]he seriousness of the disease or condition that is to be treated with the drug[,] the expected benefit of the drug with respect to such disease or condition,” and “[t]he seriousness of any known or potential adverse events.”²⁹⁶

Notably, the considerations here all seem health-related: Benefits must relate to the seriousness of the disease or condition, and elimination of that

293. 21 U.S.C. § 355(d) (2012).

294. *Safe*, MERRIAM-WEBSTER, https://www.merriam-webster.com/dictionary/safe?utm_campaign=sd&utm_medium=serp&utm_source=jsonld [<https://perma.cc/V76T-gYqj>].

295. 21 U.S.C. § 355-1(a)(1).

296. *Id.*

disease or condition—a health related effect. (Note that the effect could be indirect, such that risk compensation might be taken into account. A drug that increased HIV prevalence due to risk compensation would fail to produce benefits). Similarly, adverse events relate to health. As the statute describes elsewhere, adverse events are “health-related event associated with the use of a . . . drug that is adverse.”²⁹⁷ Given that REMS turn on health related considerations, we might conclude that the overall “safety” concerns the statute is concerned with are also health related.

Another reason for that conclusion can be gleaned from another aspect of the approval process—the setting of approval fees. Apart from the actual approval of the application, another important aspect of the drug approval process is the setting of approval fees. The statute allows the Secretary to “grant a waiver or reduction of a fee” in the interest of public health.²⁹⁸ Again, public health is not clearly defined in the statute, although the Secretary must take action to protect the public health in many other contexts that I do not discuss.²⁹⁹

The term public health, however, is quite broad. Turning again to Merriam Webster, the term refers to “the art and science dealing with the protection and improvement of community health by organized community effort and including preventive medicine and sanitary and social science.”³⁰⁰ “Community health,” “preventive medicine,” “social science,” are all terms susceptible to broad interpretation. Similarly, in *Whitman v. American Trucking*, as described above, Justice Breyer endorsed a broad approach, opining that reducing income by regulation posed a “public health” risk.³⁰¹ Nonetheless, the underlying goal appears clear—improving the health of the community and the public.

Thus, read in context with other approval-related provisions in the same subchapter, the broad “safety” criterion that governs drug approval appears to encompass only health related considerations. On one hand, health is a broad concept in many ways. However, on the flip side, the Secretary cannot very plausibly consider non-health related criteria.

297. *Id.* § 379aa. Although this section does not concern drug approval, there is no indication that Congress sought to vary the meaning of the term.

298. *Id.* §§ 379h(d), 379j.

299. *Id.* § 360ii(a) (“The Secretary shall establish and carry out an electronic product radiation control program designed to protect the public health and safety from electronic product radiation.”); *id.* § 360bbb-3(b)(1)(C) (“[A] determination by the Secretary of a public health emergency . . . or has a significant potential to affect, national security, and that involves a specified biological, chemical, radiological, or nuclear agent or agents, or a specified disease or condition that may be attributable to such agent or agents.”).

300. *Public Health*, MERRIAM-WEBSTER, <https://www.merriam-webster.com/dictionary/public%20health> [<https://perma.cc/MC66-HZCY>].

301. *Whitman v. Am. Trucking Ass'ns*, 531 U.S. 457, 495 (2001) (Breyer, J., concurring in part).

2. Advertising/Labeling Review

Although recent Supreme Court First Amendment jurisprudence might raise doubts about the full extent of FDA power in this area,³⁰² in the statute as it is written at least, the FDA has the power to penalize “false or misleading” advertising.³⁰³ It may also require information regarding “side effects, contraindications, and effectiveness” to be included in advertising or labeling. It is fair to assume that such information concerns narrower side-effects such as physiological or chemical reactions rather than broader side-effects.³⁰⁴

In addition to this, the FDA has the authority to prereview television advertisements in certain narrow circumstances. “In conducting a review of a television advertisement under this section, the Secretary may make recommendations with respect to information included in the label of the drug . . . on changes that are . . . necessary to protect the consumer good and well-being.”³⁰⁵ A more recent statute required the FDA to consider “whether the addition of quantitative summaries . . . to . . . promotional labeling or print advertising . . . would improve health care decisionmaking by clinicians and patients and consumers.”³⁰⁶ Here, broad terms like “good and well-being,” or “health care decisionmaking” are key to deciding whether the advertisements are suitable.

This section also shows special solicitude for the needs of marginalized groups. The Secretary may also make recommendations “on statements for inclusion in the advertisement to address the specific efficacy of the drug as it relates to specific population groups, including elderly populations, children, and racial and ethnic minorities.”³⁰⁷

Although the term “efficacy” is plausibly read narrowly as the chemical effects of the drug on the individual’s body, the mandate to consider overall “good and well-being” is a broad one. The statute repeats once more that “the Secretary shall take into consideration the impact of the advertised drug on elderly populations, children, and racially and ethnically diverse communities.”³⁰⁸ The term “impact” is broader than “efficacy,” and in context should be read in tandem with “good and well-being.”

Additional legislation provides insight into the way in which the discretion might be exercised. In so doing, the FDA must “review all available scientific evidence and research on decisionmaking and social and cognitive psychology and consult with drug manufacturers, clinicians, patients and

302. See *supra* note 290 and accompanying text.

303. 21 U.S.C. § 333(g).

304. See generally Konnoth, *supra* note 135 (discussing the narrower side-effects).

305. 21 U.S.C. § 353c (providing for prereview of television advertisements).

306. *Id.* § 352 note.

307. *Id.* § 353c(b)(2).

308. *Id.* § 353c(d).

consumers, experts in health literacy, representatives of racial and ethnic minorities, and experts in women's and pediatric health."³⁰⁹

This broad mandate therefore requires the FDA to consider the cognitive and behavioral—that is indirect—behavior of drug recipients. It requires the FDA to consider criteria such as “good and well-being.” This approach suggests calibration—those criteria, applied to labeling and advertising, are notably broader than the “safety” and “public health” considerations to which the FDA is limited in making approval decisions.

3. Post Approval/Marketing Power

“[T]he Secretary may . . . require a responsible person . . . to conduct a postapproval study or studies of the drug” to assess known or feared “serious risk related to the use of the drug.”³¹⁰ “The term ‘serious risk’ means a risk of a serious adverse drug experience.”³¹¹ In turn, “serious adverse drug experience” is an adverse drug experience that results in “death or immediate risk thereof; hospitalization . . . a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;” or a condition that would require “medical or surgical intervention to prevent” any of the above events.³¹² This appears to cabin the FDA’s post-approval power to physiological reactions.

But the provisions of the statute relating to actual withdrawal broaden these powers. The FDA’s post-market power allows it to notify the public and, if necessary, provide for refunds and reimbursement, if a device “presents an imminent or substantial hazard to the public health.”³¹³ It also allows it to recall any product if there is a “substantial or imminent risk to the public health.”³¹⁴ Thus, at this key point of the post-approval stage, the FDA once more is given the authority to consider public health related concerns. However, again, we see calibration: These concerns must be “substantial or imminent,” even if they are not necessarily physiologically related.

4. Adjusting the Process

Even as the statute exhibits rough calibration, it is clear that the basis of such calibration was, if anything, intuitive, rather than clearly planned. Given the roughness of the statute’s boundary lines, an issue that is indirect, and affects only third parties might fall squarely within the safety or public health realm. The FDA might have the authority to impose severe penalties but

309. Patient Protection and Affordable Care Act, Pub. L. No. 111-148, § 3507, 124 Stat. 119, 530 (2010).

310. 21 U.S.C. § 355(o)(3)(A).

311. *Id.* § 355-1(b)(5).

312. *Id.* § 355-1(b)(4).

313. *Id.* § 360h(a)(1).

314. 42 U.S.C. § 262(d)(1); 21 U.S.C. § 360h(e).

should avoid doing so. In such circumstances, the FDA should generally rely on advertising and labeling tools as well as advisory guidance.

This is precisely the approach the FDA ended up adopting the case of PrEP for example—one of the few drugs in which it considered these other side-effects. Commentators urged the FDA to refuse approval of the drug because of these effects. But the advisory committee decided—not without some difficulty—to recommend drug approval because of its certain and immediate benefits were substantial. At the same time, the committee demanded continuous study, and several members expressed the expectation that they could return and adjust the conditions of approval depending on how drug adherence behavior played out in the real world.

Other adjustments, however, should be adopted. Some of these adjustments are clear from the PrEP approval process. First, the process for taking into account the effects I outline remains unclear to the participants. For example, after learning about adherence related problems, members of the PrEP committee noted to the FDA members that they had “questions about the questions” which the committee was supposed to answer for the FDA.³¹⁵ A clear guide on the kinds of effects the FDA and its committees should consider, ranging from social to physiological, should be used, along with an explanation regarding calibration and the considerations involved.

Second, when “other” side-effect information comes up during committee hearings, committee members should be given the power to recommend approval conditionally, and propose their own guidelines, as well as demand a list of follow up studies. In the PrEP context the committee members could not do any of this and could simply vote up and down. Members, however, emphasized the need for “implementation studies, demonstration projects, the postmarketing studies,” as well as compulsory rather than voluntary registries that would allow them to carry out the studies, in light of the testimony they had received.³¹⁶ Yet, they were unable to provide a list to the FDA of these recommendations.³¹⁷

Finally, in addition to the physiological side-effects, the FDA should prepare for each drug a list of other side-effects that it is studying, that others are studying, and that it recommends study on. This will make the process clear and transparent.

VII. CONCLUSION

Some may ask how far my claims cut—today, I might seek to apply this theory to the FDA, tomorrow, to other agencies. However, two reasons suggest that my quest for systematizing these effects should be limited to the FDA. First, unlike many other agencies, the FDA's default approach is highly

315. See 1 Truvada Hearings, *supra* note 58, at 439.

316. *Id.* at 312.

317. See *id.* at 439.

formalized and technical. Indeed, as I note above, Roscoff and Revesz point to the FDA as a model for ancillary effects assessment.³¹⁸ I simply seek to incorporate these other side-effects into an already systematized and formalized framework. Second, other agencies to my knowledge do not appear to have created a similar distinction as the FDA. As I outline above, they consider ancillary effects that come to their attention, whereas the FDA seems to draw a line between those that it considers systematically (direct, physiological, and first person) and those that it will not.

What are some examples where systematic FDA review of non-physiological, indirect, third-party harms would be valuable? Consider a few examples from Part II. The FDA would be well within its authority to make decisions about PrEP based on risk compensation behavior, since that behavior clearly has implications for public health and safety. I believe that PrEP offers benefits that outweigh any risk compensation evidence. But reasonable minds, including experts in the field, may disagree with me.

Risk compensation behavior is hard to monitor in clinical trials—only the real world allows proper collection of this information. I therefore suggest reviewing and addressing this issue post-marketing. The FDA should have mechanisms in place for continuous review of risk compensation behavior. This review can be folded into existing post-market surveillance programs that might integrate individual health and pharmacy records. We will be able to longitudinally track the incidence of STDs among individuals on PrEP with relative ease.³¹⁹

The cost concerns that arise with sofosbuvir are similarly health related. The costs of the drug have important implications for health programs such as Medicare and Medicaid, as well as for private insurance. Tentative drug price information should be available at the time of application. While the FDA might run into political roadblocks if it refused to approve an application solely because of projected price, having the information would allow it to begin discussions with stakeholders about how to limit the public health effects of drug prices if the drug were approved. And after approval, the FDA should continue to assess the public health effects of high cost drugs on the market.

318. See Roscoff & Revesz, *supra* note 117, at 1791.

319. The Truvada REMS mandates screening only for HIV, not other STDs, every three months after Truvada is prescribed. GILEAD SCIENCES, INC., CHECKLIST FOR PRESCRIBERS: INITIATION OF TRUVADA® FOR PRE-EXPOSURE PROPHYLAXIS (PREP) (2012), <https://www.fda.gov/media/86169/download> [<https://perma.cc/X57R-QYNL>]. While anecdotally, I believe that most providers screen for other STDs as well, the FDA should mandate such screening. Further, while states report STD incidence to the CDC, they do not include information about whether the patient is on Truvada. MINNESOTA CONFIDENTIAL SEXUALLY TRANSMITTED DISEASE CASE REPORT, MINN. DEP'T. OF HEALTH, https://web.archive.org/web/20180612162946/http://www.health.state.mn.us/divs/idepc/dtopics/reportable/forms/std_casereport.pdf. Reporting this information would be key to carrying out risk compensation studies.

The race related concerns that BiDil presents are harder to parse. On balance, however, the FDA's public health mandate explicitly requires it to consider the welfare of marginalized groups. The FDA should probably limit its consideration of racial concerns to that of racism in the healthcare context. Measuring the effects of drugs on social attitudes is hard and is probably best done after the drug is released. It might be helpful, for example, to attempt to monitor changes in racial attitudes among doctors who are informed of the drug. One might also test out different kinds of advertising or labeling to minimize any harmful attitudes. On the flip side, if the drug were to have important benefits—curing Tay Sachs disease for example—the FDA might decide that whatever the race implications, the drug should be marketed without further intervention.

My hope is that the approach I advocate here will pervade other FDA decisionmaking. Consider, for example, the FDA's continued ban on blood donation by many gay men.³²⁰ Although governed by a slightly different statutory scheme,³²¹ many of my recommendations here could still be taken into account. The ban, many argue, imposes stigmatic harms on gay individuals in general, for chimerical health benefits. The FDA does not appear to take into account such stigmatic harms.

More generally, taking into account non-physiological effects treats our understanding of health more realistically. When the FDA regulates only chemical effects, it perpetuates a narrow understanding of health discourse. This understanding does not conform to medical knowledge regarding the varied social determinants of health and obscures the culturally contingent decisions that shape healthcare decisionmaking. Thinking of health more broadly will help address these problems and take us further forward on the path to population wellness.

320. The FDA historically banned donation of blood by all gay men. They recently limited the ban only to those gay men who had engaged in sexual intercourse over the previous year. *Revised Recommendations for Reducing the Risk of Human Immunodeficiency Virus Transmission by Blood and Blood Products—Questions and Answers*, FDA, <https://www.fda.gov/vaccines-blood-biologics/blood-blood-products/revised-recommendations-reducing-risk-human-immunodeficiency-virus-transmission-blood-and-blood> [<https://perma.cc/MP3Q-75KR>]. Many have argued that even the new ban is problematic, given that other high-risk groups can give blood, and the FDA relies in those cases on blood screening mechanisms. I. Glenn Cohen & Eli Y. Adashi, *New Blood-Donor Policy, Same Gay Stigma*, N.Y. TIMES (May 21, 2015), <https://www.nytimes.com/2015/05/21/opinion/new-blood-donor-policy-same-gay-stigma.html> [<https://perma.cc/5XTY-Q9KE>]; see also Russell K. Robinson & David M. Frost, *The Afterlife of Homophobia*, 60 ARIZ. L. REV. 213, 217 (2018).

321. 42 U.S.C. § 262 (2012) (regulation of biologics).