

## DRUGS' OTHER ADVERSE-EFFECTS

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*The introduction of drugs onto the market can have negative effects that go far beyond any adverse physiological reaction to the drug. For example, some argue that a drug that prevents HIV transmission has led to increased promiscuity and a decline in condom usage. Hepatitis C treatments threaten to bankrupt state Medicaid programs. Another drug which purported to treat heart conditions for self-identified African-Americans was criticized for reifying racial categories. These unintended phenomena—what I refer to as drugs' other side effects—can range from unintended changes in the behavior of individuals to broader consequences for third parties or society as a whole.*

*The FDA does not systematically these consider collateral effects that do not directly operate on the physiology of the recipient of the drug in the course of its regulation. Its intervention has often been haphazard and sui generis, the result of one-off acts of political pressure, or congressional action. Similarly, while courts and scholars have long focused on the kinds of items the FDA can reach—drugs and devices—they pay less attention to another key threshold question—what that considers what kinds of problems the FDA should consider when regulating these drugs beyond physiological effects. I offer a framework within which to think of these other problems—or “side effects.” First, we can distinguish between effects that are the direct causes of drug use, and those that are indirect causes. We can also draw a spectrum of effects on third parties, ranging from those at the family, local, state, national, and even global levels. Finally, we might consider whether the effect is a health effect or a non-health effect. The practice of other agencies, administrative law scholarship, the logic of consequentialism, democratic legitimacy, and information collection counsel that the FDA take into account these other side-effects explicitly. Such an approach could also save money and engage administration-wide expertise.*

*I propose that the appropriate response would recognize a spectrum of regulatory legitimacy. I argue that the statute offers a variety of choices for FDA intervention ranging in intensity ranging from flat bans to regulating labeling or prescription guidelines. Under the flexible approach, more limited forms of intervention are usually appropriate when the effects are indirect, when third parties are involved, or when non-health issues are at stake. These criteria often determine regulatory legitimacy, expertise, and certainty.*

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## INTRODUCTION

Drugs produce side-effects—that is, unintended, incidental, consequences of ingesting the drug.<sup>2</sup> Benadryl causes drowsiness;<sup>3</sup> Zoloft causes nausea;<sup>4</sup> Warfarin might result in internal bleeding.<sup>5</sup> Sometimes such side effects are serious enough for the Food & Drug Administration (FDA) to deny approval of the drug.<sup>6</sup> 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.<sup>7</sup> Manufacturers might even market these desirable side-effects.<sup>8</sup> 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.<sup>9</sup>

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.<sup>10</sup> 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.<sup>11</sup>

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<sup>2</sup> []. Much of my concerns apply to food and devices as well. However, the cultural role food plays renders distinguishing between main and side effects impossible. See [Am. U L. Sch. Fellw]. The regulation of devices differs slightly from that of drugs—enough that clarity counsels focusing only on drugs for the purpose of this Article.

<sup>3</sup> *Benadryl, Diphenhydramine Hydrochloride- Drug Summary* PDR.NET, <http://www.pdr.net/drug-summary/Benadryl-Allergy-Liqui-Gels-diphenhydramine-hydrochloride-3514> (last visited Nov. 22, 2016).

<sup>4</sup> *Zoloft, Sertraline Hydrochloride- Drug Summary*, PDR.NET, <http://www.pdr.net/drug-summary/Zoloft-sertraline-hydrochloride-474.3608> (last visited Nov. 15, 2016).

<sup>5</sup> Deposition of: Howard W. Bremer, J.T. Eaton & Company, Inc v. Bell Laboratories Inc, Motomco Limited Corporation, Joma, Inc. and Malcolm Stack, , No. 95-C-0441 S. (W.D. Wis., 1995).

<sup>6</sup> W. Kip Viscusi and Richard J. Zeckhauser. *Regulating Ambiguous Risks: the Less than Rational Regulation of Pharmaceuticals*, 44 J.LEGAL STUD. S387 (2015).

<sup>7</sup> Christine Skopec, 6 Most Dangerous Over-the-Counter Cold Medications, WALL ST. CHEAT SHEET (July 13, 2016), <https://www.cheatsheet.com/health-fitness/dangerous-over-the-counter-cold-medications.html/>; David Warren, *Does Nyquil Help You Sleep? What You Need To Know?* WEALTH FOR MY HEALTH, <https://wealthformyhealth.com/does-nyquil-help-you-sleep/>. (last visited Nov. 22, 2016). Though it is often marketed as such.

<sup>8</sup> *United States Calming and Sleeping Market: New Insights*. Companies and Markets.com, June 9, 2015. 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. **Can't access this link** \*\*\*\*

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<sup>11</sup> ANTIRETROVIRAL, T.S., 2015. *Guideline on when to start antiretroviral therapy and on pre-exposure prophylaxis for HIV*, <http://www.emtct-iatt.org/wp-content/uploads/2015/09/WHO-Guidelines-on-When-to-Start-ART-and-PrEP-September-2015.pdf> (last visited Nov. 21, 2016); **Links for these didn't work**

Dawn K. Smith, et al., *Attitudes and Program Preferences of African-American Urban Young Adults about Pre-exposure Prophylaxis (PrEP)*, AIDS EDUCATION AND PREVENTION, 24(5) 408-421 (2012).

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.<sup>12</sup> 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.<sup>13</sup>

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.

The FDA currently, as a systematic matter at least, 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.<sup>14</sup>

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. This haphazard approach comes, in part, from a failure to examine whether and why the FDA should examine these kinds of harms, and a failure to systematize and taxonomize these harms to provide explanations for *when* the FDA should engage in certain kinds of regulation.

Part I 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

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<sup>12</sup> Travis Gasper, *A Religious Right to Discriminate: Hobby Lobby and 'Religious Freedom' as a Threat to the LGBT Community*, 3 TEXAS A&M LAW REVIEW 395 (2015).

<sup>13</sup> Michael Laufert, *Race and Population-Based Medicine: Drug Development and Distributive Justice*, 21 GEO. J. LEGAL ETHICS, 859 (2008).

<sup>14</sup> 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 regulations, the office provides a database of the cost of all new regulations. *Information Collection Review Data*, OFFICE OF INFORMATION AND REGULATORY AFFAIRS, <https://www.reginfo.gov/public/do/PRAMain.jsessionid=B2E7F59DCB150A06FA30CF988269E9D8> (last visited June 8, 2018).

regulation the FDA has engaged in so far. Part II elaborates on the conceptual categories I draw—indirect, third party, and non-health effects—and considers their ethical ramifications individually. Part III then explains why considering all these values is important. Relying on administrative law scholarship in other areas, Part III 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 IV argues that because the harms themselves exist on a spectrum, FDA action should be calibrated on a spectrum as well. FDA action can range from severe to mild, affecting manufacturers, providers, patients, and others. 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.<sup>15</sup> 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 might allow regulators and the public to openly engage with and understand these issues earlier on in the process.

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<sup>15</sup> This is not to deny the relative novelty of many drug technologies. DIY gene hacking, stem cell therapies, CRISPR, mtDNA transfer,

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.

## I. DRUG WARS

### A. *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.<sup>16</sup> The first FDA related cases to arrive in the federal courts for example, were concerned whether a particular item constituted a drug.<sup>17</sup> Courts would often look to labels as the source of the defendant’s intent; such intent, in turn, dispositively classified the drug.<sup>18</sup>

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.

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<sup>16</sup> 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.” 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.”

<sup>17</sup> In *United States v. 48 Dozen Packages, More or Less, of Gauze Bandage Labeled in Part Sterilized*, the court held that that gauze bandages were a “drug” within the definition of the Pure Food and Drugs Act. (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. In *Bradley v. United States*, mineral water was considered a “drug” when the label included a list of diseases that the water would cure, including diabetes. 264 F. 79, 82 (5th Cir. 1920).

<sup>18</sup> 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. (59 F2d 446 (1932, DC Md)). Similarly, in *Seven Cases of Eckman’s Alternative v. U.S.*, a cure all mixture was considered a “drug,” when its packaging included a notice that it “has and will cure Tuberculosis.” (239 US 510 (1916)). For a more recent treatment, see Patricia J. Zettler et al., *Closing the Regulatory Gap on Synthetic Nicotine*, *BOSTON COLLEGE LAW REV* (2018) at 18. .

<sup>19</sup> Tax and bankruptcy problems will go to other kinds of tribunals. <sup>20</sup> (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.<sup>21</sup> Others may be limited in their reach to Indian tribes,<sup>22</sup> juveniles,<sup>23</sup> or military personnel.<sup>24</sup>

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 drug. Similar criteria and distinctions appear in other jurisdictional contexts.<sup>25</sup> 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.

### B. 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.<sup>26</sup>

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<sup>19</sup> Craig Konnoth & Seth Kreimer, *Spelling Out Spokeo*, 165 U. PA. L. REV. ONLINE 47 (2016), <https://www.pennlawreview.com/online/165-U-Pa-L-Rev-Online-47.pdf> (providing a framework for understanding Article III standing after Justice Alito's majority opinion in *Spokeo, Inc. v. Robins*, in which the Justice distinguished between concrete and particularized injuries)

<sup>20</sup> See for example, ¶ 51.03 TAX COURT—ORGANIZATION AND JURISDICTION, Fed. Inc. Tax'n of Indiv. ¶ 51.03 (limiting tax court jurisdiction); 9 Am. Jur. 2d Bankruptcy § 717 (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. § 3522 Courts of Limited Jurisdiction, 13 Fed. Prac. & Proc. Juris (3d ed.). See also U.S. CONST. art. III cl. 2.

<sup>21</sup> 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. 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 (juvenile courts)

<sup>22</sup> See 18 U.S.C. § 1152 (tribal courts).

<sup>23</sup> 57 C.J.S. Military Justice § 20 (military courts).

<sup>24</sup> See, e.g., *Munaf v. Geren*, 553 U.S. 674, 680, 685-689 (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).

<sup>25</sup> 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.

<sup>26</sup> Tort and intervening cause....\*\*\*

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.<sup>27</sup> Viagra has been linked to an increase in sexually transmitted diseases (though causal effects have yet to be clarified).<sup>28</sup> Thus, some call for “greater responsibility in prescribing [erectile dysfunction] medications.”<sup>29</sup> 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 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.”<sup>30</sup>

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.<sup>31</sup> Pills that reduce the harm of HIV, by rendering it a manageable disease, may similarly reduce the perceived cost of contracting HIV.

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<sup>27</sup> 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.

<sup>28</sup> 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. Fredrick Joelving, *Viagra Popping Seniors Lead the Pack for STDs*, REUTERS.COM (July 6, 2010 7:52 AM), <http://www.reuters.com/article/us-viagra-stds-idUSTRE6652HP20100706>

<sup>29</sup> Madonna Behen, *Drugs like Viagra Linked to Higher Rates of STDs*, HEALTHDAY.COM (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>

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

<sup>31</sup> Jill Blumenthal, M.D. & Richard Haubrich M.D., *Risk Compensation in PrEP: An Old Debate Emerges Yet Again*, (2014) <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4308722/> **It looks like this was edited and published in a journal with a different title, not sure which you'd like to cite** (“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].”).



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 2/3s (the number is closer to 100%),<sup>32</sup> 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.<sup>33</sup>

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.<sup>34</sup> And at least *some* empirical evidence exists of this phenomenon in cases of both the pill and PrEP, though it is far from conclusive.<sup>35</sup>

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.<sup>36</sup> Other studies have looked at the risk compensation from Lyme disease vaccination.<sup>37</sup> Nor does risk compensation

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<sup>32</sup> Theiss, J.V., 2016. [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](#). *J. Health & Biomed. L.*, 12, pp.109-217.

<sup>33</sup> 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 (2006).

<sup>34</sup> See American Health Consultants, *CDC Stats Show Unsafe Sex Practices Are Increasing*, AIDS Alert (Apr 1, 1999), available online at <http://www.ahcpub.com/ahconline/aa.html> link didn't work for me (visited Oct 2, 2002).

<sup>35</sup> 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 protection 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, General Counsel, AIDS Healthcare Found., to the Food & Drug Admin. (March 5, 2012)); 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. 19 2234-2244, (2015) (finding that those who chose to take PrEP were more likely to have receptive condomless anal intercourse, though only 10% of men who had *not* engaged in condomless anal intercourse said they now would on PrEP, 23% reported it would decrease condom use overall, and 14% said it would increase their condom use).

<sup>36</sup> Coralia Vázquez-Otero, et al., *Dispelling the Myth: Exploring Associations between the HPV Vaccine and Inconsistent Condom Use Among College Students*, 93 PREVENTIVE MEDICINE, 147-150 (2016) <https://www.ncbi.nlm.nih.gov/pubmed/27713099> (finding that, in college students who had received the HPV vaccination, there was no correlation with any change in condom use).

<sup>37</sup> Noel T. Brewer, et al., *Risk Compensation and Vaccination, Can Getting Vaccinated Cause People to Engage in Risky Behaviors?*, 34 ANN BEHAV MED 95-9 (2007).

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.<sup>80</sup> 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.

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. Since 1992, the FDA required risk management strategies to be implemented for a handful of drugs, and encouraged voluntary strategies with respect to others.<sup>38</sup> 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.”<sup>39</sup> 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.”<sup>40</sup> The presenters noted that the clinical effectiveness studies revealed no risk compensation behavior.<sup>41</sup>

### C. 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.

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<sup>80</sup> See Viscusi, *Fatal Tradeoffs* at 234-42 (cited in note 9) (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)..

<sup>38</sup> Barbara Evans, *Seven Pillars of a New Evidentiary Paradigm: the Food, Drug and Cosmetic Act Enters the Genomic Era*, 85 NOTRE DAME L REV 419-524 (2009) at 511;<http://content.healthaffairs.org/content/26/3/664.full> this page wouldn't let me view due to security certificate, but I googled and I think this is the source: Scott Gottlieb, *Drug Safety Proposals and the Intrusion of Federal Regulation Into Patient Freedom and Medical Practice*, 26 HEALTH AFFAIRS (May/June 2007) <https://www.healthaffairs.org/doi/10.1377/hlthaff.26.3.664>.

<sup>39</sup> Hearings at 242. See also 153, 231, 239 (discussing comprehensive counseling need). [CITE to REMS\*\*\*].

<sup>40</sup> 112

<sup>41</sup> 76

In 2013, the FDA approved drugs that cure Hepatitis C, a chronic condition that affects 3 million individuals.<sup>42</sup> 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.<sup>43</sup>

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.<sup>44</sup> Overall national spending on drugs was up by about 10%, “in part due to the introduction of new drug treatments for hepatitis C.”<sup>45</sup> 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.<sup>46</sup> Such costs are historically unprecedented.<sup>47</sup>

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.”<sup>48</sup> 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.<sup>49</sup>

Other examples 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.<sup>50</sup> If PrEP transforms norms among communities where condoms were often used, so that people stop using condoms,

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<sup>42</sup> Jack Hoadley, et al., *The Cost of a Cure: Revisiting Medicare Part D and Hepatitis C Drugs*, HEALTHAFFAIRS.ORG (November 3, 2016), <http://healthaffairs.org/blog/2016/11/03/the-cost-of-a-cure-revisiting-medicare-part-d-and-hepatitis-c-drugs/>.

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<sup>44</sup> Hoadley, supra note 34.

<sup>45</sup> <http://www.imshealth.com/en/thought-leadership/quintilesims-institute/reports/medicines-use-and-spending-in-the-us-a-review-of-2015-and-outlook-to-2020>  
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<sup>46</sup> <http://www.imshealth.com/en/thought-leadership/quintilesims-institute/reports/medicines-use-and-spending-in-the-us-a-review-of-2015-and-outlook-to-2020>  
couldn't find the source on this link

<sup>47</sup> Margot Sanger-Katz, *Why the Price of Sovaldi is a Shock to the System*, NYTIMES.COM (August 6, 2014), <http://www.nytimes.com/2014/08/07/upshot/why-the-price-of-sovaldi-is-a-shock-to-the-system.html>

<sup>48</sup> Laura Fegraus & Murray Ross. *Sovaldi, Harvoni, and Why It's Different this Time*, HEALTHAFFAIRS.ORG (NOVEMBER 21, 2014), <http://healthaffairs.org/blog/2014/11/21/sovaldi-harvoni-and-why-its-different-this-time/>

<sup>49</sup> See Frequently Asked Questions about CDER, FDA.GOV <https://www.fda.gov/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/faqsaboutcder/#16> (last visited May 30, 2018). (“We understand that drug prices have a direct impact on the ability of people to cope with their illnesses as well as meet other expenses. However, FDA has no legal authority to investigate or control the prices charged for marketed drugs.”)

<sup>50</sup> Liz Highleyman, “Raw Sex”: Are the Rules Changing?, BETABLOG, (Dec. 5, 2013), <http://betablog.org/raw-sex-rules-changing/>; Rod Knight, et al., *Complex and Shifting Social Norms: Implications for Implementation of Future HIV Pre-exposure Prophylaxis (PrEP) Interventions in Vancouver, Canada*, PLOS ONE.ORG (January 12, 2016), <http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0146513>.

then individuals not on PrEP may well feel pressured not to use condoms, as commentators at the advisory committee hearings noted.<sup>51</sup> 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)<sup>52</sup> 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 food chain.<sup>53</sup> The FDA requires a statement in only some cases.<sup>54</sup> While such impact statements are rare, they do occur.<sup>55</sup>

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.<sup>56</sup>

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.”<sup>57</sup> 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.

[Two other examples to consider: Trump administration approach to generics and question of cost; opioid article by Zettler, Riley & Kesselheim\*\*\*\*]

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<sup>52</sup> 15 U.S.C. 1471

<sup>53</sup> <https://www.sciencedirect.com/science/article/pii/S0043135402002270>;  
<https://www.sciencedirect.com/science/article/pii/S0045653597003548>

<sup>54</sup> 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...” <https://www.fda.gov/downloads/Drugs/Guidances/ucm070561.pdf> Find numbers\*\*\*\*.

<sup>55</sup> <https://www.sciencedirect.com/science/article/pii/S030440179390163H>

<sup>56</sup> See, National Institute of Health, *Stop the Spread of Superbugs: Help Fight Drug-Resistant Bacteria*, NEWS IN HEALTH (February 2014) <https://newsinhealth.nih.gov/issue/feb2014/feature1> (“[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.’”).

<sup>57</sup> Extralabel Drug Use in Animals, 61 Fed. Reg. 57732 (1996).

*D. 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 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 example. The period's "[f]irst political drug approval" was RU-486, 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.<sup>58</sup> 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.<sup>59</sup>

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.<sup>60</sup> But apparently responding to pressure from Congress,<sup>61</sup> the FDA prohibited the import of RU-486.<sup>62</sup> A district court found this decision "based not [on] any bona fide concern for the safety of users of the drug, but on political" considerations.<sup>63</sup> 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 the product,"<sup>64</sup> prompting the committee chairman to observe that the FDA was "basically offering management by intuition to the American people."<sup>65</sup>

The next year, on the second day of his presidency, Bill Clinton directed the FDA to rescind the import ban on RU486.<sup>66</sup> However, the holder of the patent could find no manufacturer for the drug, delaying its approval by 3 years. And the new FDA Commissioner's confirmation was denied—until she assured Republican leaders that she would not actively facilitate the final approval of the drug.<sup>67</sup> The FDA did, ultimately, fast track the drug's approval, under a

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<sup>58</sup> James G. Dickinson, *Mifeprex: FDA's First "Political" Drug Approval*, MED. MKTG. & MEDIA, (2000), at 14.

<sup>59</sup> Lars Noah, *A Miscarriage in the Drug Approval Process?: Mifepristone Embroils the FDA in Abortion Politics*, 36 WAKE FOREST L. REV. 571, 572-739 (2001).

<sup>60</sup> Import alert See FDA, REGULATORY PROCEDURES MANUAL, Ch. 9-71-30(C) (1997), available at [http://www.fda.gov/ora/compliance\\_ref/rpm\\_new2/](http://www.fda.gov/ora/compliance_ref/rpm_new2/); 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 (2000).

<sup>61</sup> Letter from Rep. Robert K. Dornan (Ca.) et. al., to Dr. Frank Young, Commissioner, Food and Drug Administration (May 5, 1989).

<sup>62</sup> *Automatic Detention of Abortifacient Drugs*, FDA IMPORT ALERT No. 66-47 (June 6, 1989).

<sup>63</sup> [Benten, 799 F. Supp. at 286](#); 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).

<sup>64</sup> *RU486: The Import Ban and Its Effect on Medical Research: Hearings Before the Subcomm. on Regulation, Business Opportunities, and Energy, of the House Comm. on Small Business*, 101st Cong., 2d Sess. 35-52 (1990) hereinafter *RU486 Hearings* (FDA gave reasons for ban) (statement of Ronald Chesemore).

<sup>65</sup> (statement of Chairman Wyden).

<sup>66</sup> Memorandum on Importation of RU-486, 29 Weekly Comp. Pres. Doc. 89 (Jan. 22, 1993).

<sup>67</sup> See Judy Mann, *We Need the Abortion Pill Now*, WASH. POST, June 23, 2000, at C9; Katherine Q. Seelye, *House Votes to Block FDA on Approval of Abortion Pill*, N.Y. TIMES, June 25, 1998, at A20.

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.<sup>68</sup>

The RU486 saga was quickly followed by drama over Plan B during the George W. Bush administration. 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.”<sup>69</sup> 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.<sup>70</sup> Notably, Bush 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.<sup>71</sup>

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.<sup>72</sup> This drug was approved to treat cardiac failure in African Americans, and was the first drug to be targeted to a specific racial group.<sup>73</sup>

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.”<sup>74</sup> The trials for BiDil included a large cohort of African-

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<sup>68</sup> See [57 Fed. Reg. 58,942, 58,958 \(1992\)](#) (codified as amended at 21 C.F.R. pt. 314(H) (2001)); U.S. Food and Drug Administration, Center for Drug Evaluation and Research, *Prescriber’s Agreement Form*, <http://www.fda.gov/cder/drug/infopage/mifepristone/default.htm> link didn’t work for me (Aug. 1, 2001) (emphasis added).

<sup>69</sup> [Tummino v. Von Eschenbach, 427 F. Supp. 2d 212, 220 \(E.D.N.Y. 2006\)](#)

<sup>70</sup> U.S. Gov’t Accountability Office, No. GAO-06-109, *Food and Drug Administration: Decision Process to Deny Initial Application for Over-the-Counter Marketing of the Emergency Contraceptive Drug Plan B Was Unusual* 7-11 (2005), 42-46 app. III (providing timeline of internal FDA actions on the Plan B OTC switch application); id. at 51-52 app. V (memorandum from Office of New Drugs’ Director noting moral concerns regarding adolescent sexual activity and parental control raised by the Plan B OTC switch application); e), *Supra* note for import. <http://www.gao.gov/new.items/d06109.pdf>

<sup>71</sup> Rick Weiss, *New Status for Embryos in Research*, WASH. POST, Oct. 30, 2002, at A1.

<sup>72</sup> 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, 928 (2014).

<sup>73</sup> Stephanie Saul, *FDA Approves Heart Drug for African Americans*, NYTIMES (June 24, 2005), [http://www.nytimes.com/2005/06/24/health/fda-approves-a-heart-drug-for-africanamericans.html?\\_r=0](http://www.nytimes.com/2005/06/24/health/fda-approves-a-heart-drug-for-africanamericans.html?_r=0).

<sup>74</sup> 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 Roberts, Is Race-Based Medicine Good for Us?: African American Approaches to Race, Biomedicine, and Equality* JLME 537 (2008).

<sup>75</sup> Emily S. Stopa, *Harnessing Comparative Effectiveness Research to Bend the Cost Curve and Achieve Successful Health Reform: An Assessment of Constitutional Barriers to Limiting Health Care Treatment Options*, 13 U. PA. J. CONST. L., 815 (2010).

Americans as the result of intensive recruitment.<sup>76</sup> 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.<sup>77</sup> And as Dorothy Roberts observes, such “racial medicine” can divert attention away from these root causes “toward genetic explanations and technological solutions.”<sup>78</sup> 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.”<sup>79</sup> Without such affirmation, racial categories remained fluid. As one witness before the FDA Advisory Committee asked: “What 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 BiDil?”<sup>80</sup> 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.”<sup>81</sup> 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.<sup>82</sup> 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.

### E. Shortcomings

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<sup>76</sup> Sharona Hoffman, *'Racially-Tailored' Medicine Unraveled*, 55 AMERICAN UNIVERSITY LAW REVIEW 395-452 (2005); Britt M. Rusert, and Charmaine D. M. Royal, *Grassroots Marketing in a Global Era: More Lessons from BiDil*, 39 THE J. L., MED. & ETHICS 79-90.

<sup>77</sup>

<sup>78</sup> Id.

<sup>79</sup> Id.; Carolyn Johnson, *Should Medicine Be Colorblind?*, BOS. GLOBE, Aug. 24, 2004, at 1-2; Dorothy E. Roberts, *Law, Race, and Biotechnology: Toward a Biopolitical and Transdisciplinary Paradigm*, 9 ANNUAL REVIEW OF LAW AND SOCIAL SCIENCE, 149-166 (2013); Erik Lillquist and Charles A. Sullivan, *Legal Regulation of the Use of Race in Medical Research*, 34 JL MED. & ETHICS, 535 (2006). Howard Brody and Linda M. Hunt *BiDil: Assessing a Race-Based Pharmaceutical*, 4 ANN. FAM. MED., 556-560 (2006).

<sup>80</sup> [Hearing Transcript\*\*\*].

<sup>81</sup> Abigail Zuger, MD., *From a Bang to a Whimper: A Heart Drug's Story*, NYTIMES.COM, (Dec. 24, 2012), <http://www.nytimes.com/2012/12/25/science/from-bang-to-whimper-a-heart-drugs-story.html>.

<sup>82</sup> [Transcript \*\*\*]. Osagie K. Obasogie, *Return of Biological Race: Regulating Innovations in Race and Genetics through Administrative Agency Race Impact Assessments*, *The* 22 S. Cal. Interdisc. LJ 1. (2012); Britt M. Rusert. and Charmaine D. Royal *Grassroots Marketing in a Global Era: More Lessons from BiDil*, 39 THE JOURNAL OF LAW, MEDICINE & ETHICS, 79-90 (2011); Shiloh Krupar and Nadine Ehlers, *Biofutures: Race and the Governance of Health*, 35 ENVIRONMENT AND PLANNING D: SOCIETY AND SPACE 222-240(2017).

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 (c) 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.<sup>83</sup> 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 unanimous in their opinion that risk compensation would be a serious problem.<sup>84</sup> They cited studies in which a sizeable number of respondents acknowledged that they would stop using condoms were PrEP widely available.<sup>85</sup> 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.<sup>86</sup> 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.<sup>87</sup> However, their concerns were never discussed. Yet another commenter discussed how PrEP would change the norms of condom use: “it will make it even harder for people, especially women, to” negotiate condom use with their partners to “protect themselves.”<sup>88</sup> 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: “clients are capable of making healthy decisions for their own lives

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<sup>83</sup> Id. at 76.

<sup>84</sup> 262, see also 330, 331 (“Using this treatment as a preventive measure for HIV will be seen as a medical condom.”); 264, 265, 269,331

<sup>85</sup> Id. at 262

<sup>86</sup> Those with suppressed viral loads are unable to transmit the virus. CITE\*\*

<sup>87</sup> 283: “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” See also 318.

<sup>88</sup> 322



[and]... don't require our paternalizing them.”<sup>89</sup> 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.”<sup>90</sup> 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).<sup>91</sup>

## 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].”<sup>92</sup> 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.”<sup>93</sup> The members sought “good data about what's going on” with respect to non-physiological criteria not based on “voluntary [self-]assessment.”<sup>94</sup> 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?”<sup>95</sup> 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.

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

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<sup>89</sup> 341-42; 509 haunted 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”

<sup>90</sup>

197 Day two

<sup>91</sup> 1-10

<sup>92</sup> Padian 440, 505

<sup>93</sup> Morrato 482.

<sup>94</sup> Padian 470

<sup>95</sup> 72

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.

## II. DEFINING CATEGORIES

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.

### A. *Indirect Harms*

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.<sup>96</sup>

There are two approaches to this distinction. The first is the “purpose” approach, which bioethicist Dan Brock advocates. Brock explains: “the direct benefits of opening a large, new primary care clinic [is] improved primary health care..., the consequence that the hospital's cafeteria is no longer unprofitable ...is an indirect benefit, even if it may be as closely causally related.”<sup>97</sup>

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.<sup>98</sup> 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

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<sup>96</sup> Rascoff and Revesz definition, Chi. L. Rev. (2002), 1771 provide an example: “the very act of regulating the target risk itself brings about ancillary risks.” They 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.” Substitution effects are likely mitigated in the drug context given the FDA’s control over approval.

<sup>97</sup> Dan Brock, *Separate Spheres and Indirect Benefits*, Cost Effectiveness and Resource Allocation 1:4 (Feb. 26, 2003) [http://download.springer.com/static/pdf/7/art%253A10.1186%252F1478-7547-1-4.pdf?originUrl=http%3A%2F%2Fresource-allocation.biomedcentral.com%2Farticle%2F10.1186%2F1478-7547-1-4&token2=exp=1492113850~acl=%2Fstatic%2Fpdf%2F7%2Fart%25253A10.1186%25252F1478-7547-1-4.pdf\\*~hmac=bf1d943f0ea8280d7c028345c43191e5153ab6ea0cca3fd83290aba3bec4721](http://download.springer.com/static/pdf/7/art%253A10.1186%252F1478-7547-1-4.pdf?originUrl=http%3A%2F%2Fresource-allocation.biomedcentral.com%2Farticle%2F10.1186%2F1478-7547-1-4&token2=exp=1492113850~acl=%2Fstatic%2Fpdf%2F7%2Fart%25253A10.1186%25252F1478-7547-1-4.pdf*~hmac=bf1d943f0ea8280d7c028345c43191e5153ab6ea0cca3fd83290aba3bec4721)

<sup>98</sup> As in the regulatory context. See, e.g., Roscoff & Revesz, *supra* note at 1766-67.

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.<sup>99</sup>

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.

Brock examines the ethics of considering indirect effects. Consider choosing between saving the life of a doctor or a murderer. The doctor, if saved, would heal numerous people; the murderer would kill again.<sup>100</sup> Drawing from the work of others, Brock presents two key reasons why one should not consider indirect effects in such circumstances.<sup>101</sup>

First, treating people differently disrespects their equal moral worth as humans with “equal moral claims” to basic rights such as healthcare. Second, valuing people based on what they can provide society treats them as means (to these other purposes) and therefore violates Kantian principles. Accordingly, individuals should be given access to the resource equally. In situations where there is not enough medication to go around, he argues, the system should offer individuals an equal *chance* to get access to the medication—for example, through a lottery system.<sup>102</sup>

Whether Brock’s equity objections here are relevant depends, first, on the nature of the FDA intervention. 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.

Problems arise, however, if the FDA were to discriminate *among* patients, a course of action that some of my recommendations in Part IV contemplate. For example, the FDA could instruct providers to refuse to provide drugs to someone who is likely to carry out increased risk compensation. Assume that Person A

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<sup>99</sup> See 21-101 Personal Injury--Actions, Defenses, Damages § 101.06; Tampa Elec. Co. v. Jones, 190 So. 26, 27 (Fla. 1939)

<sup>100</sup> The example is mine, the reasons are Brock’s.

<sup>101</sup> Brock lays these out as three reasons, but they effectively boil down to two. He presents the equality claim as two separate claims: treating people differently disrespects their equal moral worth as humans. Second, it disregards their “equal moral claims” as human beings to obtaining health rights.

<sup>102</sup> 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 Glenn Cohen, also SEP article and Brock 2002.

uses a condom without PrEP but would not use one with PrEP. Person B would not use a condom either way. Under that criterion, we would provide PrEP to Person B but not A, as only the latter risk compensates. This is arguably the optimal outcome from a utilitarian standpoint. The side-effect may outweigh the benefit in the case of Person A as he would stop using condoms, but not in the case of Person B. But using increased risk compensation as a criterion might mean that we deny the drug to A who is arguably *more* morally responsible than B as a general matter. Accordingly, would it be appropriate to distinguish in this way between individuals?

First, Brock's equality presumption would *require* us to take into account indirect effects in a complex world in some cases at least. 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 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, 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.

But outside the allocational context, non-consequentialism might well forbid the FDA from considering indirect effects. However, indirect effects would simply be replaced with some other moral criterion. A consequentialist would save the doctor and leave the murderer precisely because she cares only about effects. Because of the differing indirect effects of saving them, the doctor and the murderer are not similarly situated. But it is also unlikely that a Kantian would see the doctor and the murderer as similarly situated. They have different moral deserts. 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.<sup>103</sup>

What is key is that these other approaches do not demand *equal* treatment for the doctor and murderer as Brock seems to suggest. 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

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<sup>103</sup> See Glenn Cohen for an overview of different ethical approaches. 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. 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.

criteria, however, are better relegated to “non-health” related considerations that I raise in the final Section.

Suffice it to say, however, that 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. The value pluralism inherent in policy decisions requires the FDA to consider these indirect effects as well as other, non-health related criteria that I describe further below.

### *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.<sup>104</sup> 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.<sup>105</sup>

In considering the duties the FDA might owe to these third parties, it is useful to distinguish between micro, meso, and macro-ethics.<sup>106</sup> 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 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

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<sup>104</sup> 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.

<sup>105</sup> 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.

<sup>106</sup> [bioethics example\*\*\*]. This definition maps on to similar approaches in sociological inquiry and political theory as well. CONTEMPORARY SOCIOLOGICAL THEORY at 27 (Craig Calhoun et al. eds., 3d ed. 2012); JOHN T. ROURKE, *Levels of analysis, in* INTERNATIONAL POLITICS ON THE WORLD STAGE, (10th ed. 2005).

than those owed to one's roommate.<sup>107</sup> 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) who 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.<sup>108</sup> The obligations are those of friendship and love. The FDA's intervention would displace the primary obligations between intimates. 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.<sup>109</sup> One can imagine a range of other examples—Hepatitis C patients would benefit from even an expensive drug,

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<sup>107</sup> [DISCUSS FURTHER—OBLIGATIONS OWED TO STRANGERS\*\*\*\*]

<sup>108</sup> Sarah EM 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*, Health Research and Policy Systems, 10:32 (2012), (discussing the potential for misunderstanding and misinterpretation at the meso-level).

<sup>109</sup> Leah Sammons, *Racial Profiling: Not Always a Bad Thing*, Chicago Defender, February 9, 2006; Gary Puckrein, *BiDil: From Another Vantage Point*, 25 HEALTH AFFAIRS w368-w374 (2006)\*\*\*

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.<sup>110</sup>

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 stretching their budgets and limiting coverage.<sup>111</sup> 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 on PrEP might experience consequences if their adherence falters or they lose access to the drug—if they lose insurance for example.<sup>112</sup> 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. The racist message that the approval or prescription of a drug like BiDil produces would be a direct but non-health harm.<sup>113</sup> 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 effects: (1) Is there a coherent line to draw between health and non-health concerns? If so, (2) can the FDA ethically consider non-health concerns in making its decision?

Dan Brock has sought to draw the line between health and non-health effects. The nature of the effect depends on what sphere they are a part of. Pointing to the work of political theorist Michael Walzer, Brock concludes that the nature of a sphere is defined by “[t]he purposes of [its] activities” which in

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<sup>110</sup> See Jason Potter Burda, *When Condoms Fail: Making Room Under the ACA Blanket for PrEP HIV Prevention*, 52 SAN DIEGO L. REV. 171, 188 (2015) (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., 119-127 (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).

<sup>111</sup> Ed Silverman, *State Medicaid Programs Continue to Restrict Access to Hepatitis C Drugs*, STAT NEWS (November 14, 2016), <https://www.statnews.com/pharmalot/2016/11/14/medicaid-hepatitis-gilead/>.

<sup>112</sup> Cf. Allison Hoffman, *Reimagining the Risk of Long-Term Care*, 16 YALE J. HEALTH POL’Y L. & ETHICS 16-48 (2016).

<sup>113</sup>

turn, are determined both subjectively, “by the actual purposes of those engaged in them,” as well as objectively based on social “convention[s]...[and] social meanings they have in a community.”<sup>114</sup>

There is, accordingly, a discernible, albeit culturally constructed, bounded “health sphere.” Culturally and socially created rules and conventions, many embedded in law, will define the boundaries and content of this sphere. At the same time, the social meanings of different activities depend on context. “[I]n a non-democratic caste society, political elections have a different social meaning than they do in democracies.”<sup>115</sup> And meaning can change: one can persuade the “members of his society to revise their understanding of the nature and purpose of the health care system to include [various] goals,” thus changing the reach of “health.”

A recent article by law professor Zack Buck seeks to shift boundaries in exactly that way. The article explores the concept of “financial toxicity” that has appeared in the medical literature. 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. 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. 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.”<sup>116</sup> 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.<sup>117</sup> Interestingly, Buck 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.<sup>118</sup> I would argue that the drug regulatory apparatus also has a role here.

To be sure, moving boundaries are not without their problems. If financial toxicity should be understood to be a medical phenomenon, why should it be restricted only to contexts where the financial harm is caused by medical treatment? The studies on which Buck relies suggest that any kind of penury is toxic and unhealthful for the individual. But that, perhaps, is the point of Buck’s argument, which demonstrates incremental shifting of social context.

Indeed, Buck’s argument is of a similar cloth to a broader literature on what’s called “social determinants of health.” These are “the structural

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<sup>114</sup> Brock, *supra* note.

<sup>115</sup> *Id.*

<sup>116</sup> See Isaac D. Buck, *The Cost of High Prices: Embedding an Ethic of Expense into the Standard of Care*, 58 B.C. L. Rev. 101, 142, (2017).

<sup>117</sup> *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 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”).

<sup>118</sup> *Id.*



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.<sup>119</sup> 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.<sup>120</sup>

Given this degree of contingency, it is admittedly, hard to make any stable ethical claims about the reach of the FDA across spheres. By reifying racism (if that is, in fact, what it did), Bi-Dil would affect a social determinant of health. It would increase minority stress and discrimination resulting in negative health outcomes across a certain group.<sup>121</sup>

As a practical matter, though, one can draw a rough line dividing social spheres even while recognizing their contingent and constructed nature. This brings us to the second question: Can health entities properly take into account harms occurring beyond the health sphere? Should the FDA consider the racial effects of BiDil when approving it, or should it only take into account the health-related effects of the drug? Brock provides an answer based on institutional competence. Each institution should take into account the kinds of effects it is designed to solve. So the legislature must consider a range of health and non-health effects, but a hospital administrator would consider only health related goals.

But how do we know what a particular institution’s competence is? Brock does not elaborate, but here too, I believe, we must rely on a constructivist account. The considerations an institution should take into account depend on how it was created. If a body was created to be a federal agency in charge of a particular health related issue, then that is its competency. Laws will help us determine what the nature and purpose of a particular agency is supposed to be.<sup>122</sup>

This was, in fact, the approach taken by the Supreme Court in *POM Wonderful v. Coca-Cola*.<sup>123</sup> 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 Court concluded that

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<sup>119</sup> Samantha Artiga & Elizabeth Hinton, *Beyond Health Care: The Role of Social Determinants in Promoting Health and Health Equity*, HENRY J. KAISER FAMILY FOUNDATION (May 10, 2018), <http://kff.org/disparities-policy/issue-brief/bevond-health-care-the-role-of-social-determinants-in-promoting-health-and-health-equity/>.

<sup>120</sup> IV. MEASURING THE IMPLEMENTATION AND HEALTH EFFECTS OF LAW: Eileen O’Keefe & Alex Scott- Samuel, *Human Rights and Wrongs: Could Health Impact Assessment Help?*, 30 J.L. MED. & ETHICS 734 (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/> (last visited Dec. 17, 2010); see also R. Quigley et al., *Health Impact Assessment: International Best Principles*, Int’l Ass’n for Impact Assessment (2006), <http://www.iaia.org/publicdocuments/special-publications/SP5.pdf> link didn’t work for me (summarizing health impact assessments).

<sup>121</sup> Minority stress literature.\*\*\*

<sup>122</sup> In practice, I’m persuaded by Glenn Cohen’s suggestion that, in analogous contexts, institutions are often meant, and expected, to adopt a “hybrid” approach that prioritizes their particular goals, without being blind to broader effects.

<sup>123</sup> 134 S. Ct. 2228, 2231 (2014)

“the Lanham Act and the FDCA ... each has its own scope and purpose. 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.” For this, the Court relied on an analysis of the statutory provisions of both statutes. Accordingly, our task is to look to how the law defines the FDA’s purposes and functions.<sup>124</sup>

### III. THE 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, This Part now turns to the overall advisability of considering such side-effects in general. It argues that overall, considering such effects conforms to administrative analysis, transparency, and information gathering values, and that objections are limited.

#### A. *Consequentialism*

Scholarship, case law, and regulatory approaches in the administrative law field overwhelmingly advocate for consequentialist reasoning, in particular, cost-benefit analysis (CBA), as a necessary guide to agency decisionmaking.<sup>125</sup> 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.<sup>126 127</sup>

As scholars and judges explain, the logic of consequentialism and, relatedly, CBA, means that an intervention whose ancillary costs are heavy enough should not be made even if it achieves the desired goal.<sup>128</sup> 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...”

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.<sup>129</sup> Indeed, Samuel Rascoff and Ricky Revesz, in their important article on ancillary effects, explicitly use the term “side effects”

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<sup>124</sup> I. Glenn Cohen, *Rationing Legal Services*, 5 THE JOURNAL OF LEGAL ANALYSIS, 221-307 (2013) at 250.

<sup>125</sup> See e.g., Revesz Book.

<sup>126</sup> Id. At 1767

<sup>127</sup> Samuel J. Rascoff & Richard L. Revesz, *The Biases of Risk Tradeoff Analysis*, 69 THE UNIVERSITY OF CHICAGO LAW REVIEW 1763 (2002).

<sup>128</sup> Rascoff and Revesz canvas the literature in some detail. See id. At 1781-89

<sup>129</sup> With the exception of Rascoff and Revesz who argue that the FDA does not consider “side benefits” of drugs as well as unintended costs. Id.

to refer to ancillary costs—unconsciously, perhaps, evoking the term so common to FDA assessment. 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,<sup>130</sup> 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.<sup>131</sup> 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 interreliant. 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.<sup>132</sup>

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 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.” This, in turn, he noted, citing the \$7.25 million figure, could cause a loss of life. 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,<sup>95</sup> as do Judges Easterbrook,<sup>92</sup> and Posner.<sup>93</sup>

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.<sup>133</sup> As its letter to the agency announcing its decision explained, citing Judge Williams’s then recently issued opinion, “[i]f government regulations force firms

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<sup>130</sup> Rascoff & Revesz carry out such categorization. My criticisms appear in notes \_\_\_ above.

<sup>131</sup> Cass R. Sunstein, *Health-Health Tradeoffs*, 63 U CHI L REV 1533 (1996). As Roscoff & Revesz at 1778 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.

<sup>132</sup> Ralph L. Keeney, *Mortality Risks Induced by Economic Expenditures*, 10 RISK ANAL 147 (1990).

<sup>95</sup> See *American Trucking*, 531 US at 490-96 (Breyer concurring in part and concurring in the judgment). We discuss Justice Breyer's concurrence in the text accompanying notes 153-61.

<sup>89</sup> See Breyer, *Breaking the Vicious Circle* at 23 & n 119 (cited in note 5).

<sup>92</sup> See *International Union, UAW v Johnson Controls, Inc.*, 886 F2d 871, 918 (7th Cir 1989) (en banc) (Easterbrook dissenting) (arguing that removing women from jobs in which they run the risk of lead exposure might create more overall risk for their children because "the net effect of lower income and less medical care could be a reduction in infants' prospects"), revd, 499 US 187 (1991).

<sup>93</sup> See *American Dental Association v Martin*, 984 F2d 823, 826 (7th Cir 1993) (Posner) (reasoning that OSHA--by not taking into account lives sacrificed because of increased health care costs passed on to consumers--exaggerated the number of lives saved by mandatory workplace precautions against AIDS).

<sup>133</sup> See Rascoff & Revesz, 1787

out of business or into overseas production, employment of American workers will be reduced, making workers less healthy by reducing their incomes.”<sup>14</sup> 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 affects appears even when there is no relationship between wealth and health to be drawn. In *Corrosion Proof Fittings v EPA*,<sup>77</sup> the Fifth Circuit struck down an EPA rule that sought to reduce asbestos exposure. 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 consider the toxicity of likely substitutes thus deprives its order of a reasonable basis."<sup>7</sup>

Similarly, in *Competitive Enterprise Institute v National Highway Traffic Safety Administration*, (*CEI*)<sup>71</sup> plaintiffs challenged a fuel standards regulation. 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.<sup>72</sup> "By making it harder for consumers to buy large cars, the 27.5 miles per gallon (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."<sup>73</sup>

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,’ taking into account technological feasibility, economic feasibility, the effect upon fuel economy of other federal motor vehicle standards,

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<sup>141</sup> Regulatory Review Process, 138 Cong Rec at S 3809 (cited in note 138).

<sup>77</sup> [947 F2d 1201 \(5th Cir 1991\)](#).

<sup>78</sup> [Id. at 1221](#). The approach to risk tradeoffs embodied in these two cases should be contrasted with the treatment of this issue in the previous decade. For example, [Environmental Defense Fund, Inc v EPA, 510 F2d 1292 \(DC Cir 1975\)](#), presented numerous challenges to the EPA's decision to suspend the registration and ban the manufacture of the pesticides aldrin and dieldrin. See [id. at 1295-96](#). Shell Chemical Company challenged the ban, arguing among other things that "because heptachlor [the likely substitute] presents an identical cancer risk . . . the Administrator's suspension of aldrin/dieldrin does not 'prevent' an imminent hazard as required by the statute." [Id. at 1303](#). Judge Leventhal rejected that rationale, reasoning, "There is no law that says that all evils must be attacked at the same time and at the same rate." [Id.](#)

<sup>71</sup> [956 F2d 321 \(DC Cir 1992\)](#).

<sup>72</sup> 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 [Competitive Enterprise Institute, 956 F2d at 327](#).

<sup>73</sup> [Competitive Enterprise Institute, 956 F2d at 326](#).

and the need of the nation to conserve energy.”<sup>134</sup> 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. 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.”

The consequentialist logic of agency review and CBA therefore supports consideration of indirect, third-party, non-field specific considerations. It is 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. 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 legitimacy concerns.<sup>135</sup>

In general, when agencies are prohibited from considering certain important characteristics, they do so anyway, but in a surreptitious manner. To take an analogous example, in some contexts, agencies are forbidden from considering the economic cost of regulation.<sup>136</sup> Nonetheless, as one senior official explained, “it is foolish to pretend that economic concerns will not enter into the decision-making process.” Thus, “it is positively deceitful to require that the economic considerations which do influence the Administrator's decision be hidden from public view.”<sup>138</sup> Another senior official explains that such an approach “should never be tolerated in an open and democratic society and that has perversely impeded some of the...objectives the Agency is supposed to promote.”<sup>319</sup>

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<sup>134</sup> *COMPETITIVE ENTERPRISE INSTITUTE, and Consumer Alert, Petitioners, v. NATIONAL HIGHWAY TRAFFIC SAFETY ADMINISTRATION* (quoting 15 U.S.C. § 2002(e) (listing factors); 15 U.S.C. § 2002(a)(4) (granting Secretary of Transportation discretion to amend CAFE standard); 49 C.F.R. § 1.50(f) (delegating authority to NHTSA).

<sup>135</sup> Michael A. Livermore & Richard L. Revesz, *Rethinking Health-Based Environmental Standards*, 89 N.Y.U. L. REV. 1184, 1186–87 (2014)

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<sup>318</sup> *Clean Air Act Oversight: Hearings Before the Comm. on Env'tl. and Pub. Works*, U.S. Senate, 97 Cong. 199 (1981) (statement of George C. Eads); see also George C. Eads, *The Confusion of Goals and Instruments: The Explicit Consideration of Cost in Setting National Ambient Air Quality Standards*, in *TO BREATHE FREELY: RISK, CONSENT, AND AIR 228-29* (Mary Gibson ed., 1985) (“In order to develop a standard that would stand up in court, [the EPA Administrator] was forced to pretend (though the pretense was relatively transparent in this case) that costs did not play an overt role in his decision...the public lost the chance to examine the role that cost - as opposed to other factors - did play in influencing his judgment.”).

<sup>319</sup> C. Boyden Gray, *The Clean Air Act Under Regulatory Reform*, [11 TUL. ENVTL. L.J. 235, 235 \(1998\)](#).

While these commenters addressed the de facto consideration of economic costs, “the plain fact” is that political and value judgments are also a part of the agency process in a democratic society.<sup>137</sup> To take one example, the OIRA decision to suspend workplace safety regulation review that I discuss above took place against a backdrop where the White House had declared a 90 day moratorium on all new federal regulations.<sup>138</sup> In response, the agency’s whose regulations were suspended suggested that OMB should publish notice of such a policy change in the Federal Register in the interests of transparency.<sup>139</sup>

The FDA is hardly above the vagaries of political fortunes. As scholars have documented, changes of administration frequently reflect changes in values. As FDA expert Lars Noah notes, “Most observers doubted that the FDA would have approved [RU486] before Clinton came into office, and, had there been any further delay, it seems unlikely that the agency would have approved it once George W. Bush entered the White House.”<sup>140</sup> The RU-486 controversy was hardly the only time politics entered the FDA decisionmaking process.<sup>141</sup>

For democratic accountability to mean anything, administrative judgments, whether based on values or something else, require explicit and open consideration. As Roscoff and Revesz note in CBA, “[t]he unacknowledged consideration of a factor ... has obvious negative consequences for ... transparency [and] accountability.” “[R]eason giving,” they note “is so ‘central to U.S. administrative law and practice.’” Theories of agency legitimacy, accountability (to Congress, the judiciary, and even internally to other administrative entities), and deliberative democracy,<sup>142</sup> promote transparency in government reasoning.<sup>324</sup>

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<sup>137</sup> Id.

<sup>138</sup> 138 Cong Rec. S3807 (March. 18, 1992).

<sup>139</sup> Id.

<sup>140</sup> Noah supra note .

<sup>141</sup> See Alexander Morgan Capron, *Does Assessment of Medical Practices Have a Future?*, [82 VA. L. REV. 1623, 1625 \(1996\)](#) (describing the FDA’s initial resistance, during President Reagan’s first term in office, to approving alphafetoprotein test kits to screen for neural tube defects because it might encourage unnecessary abortions); Lars Noah, *Interpreting Agency Enabling Acts: Misplaced Metaphors in Administrative Law*, [41 WM. & MARY L. REV. 1463, 1529 \(2000\)](#) (noting that “President Clinton got behind the FDA’s previously unthinkable initiative [to regulate tobacco products] as a campaign gambit”); Steven R. Salbu, *HIV Home Testing and the FDA: The Case for Regulatory Restraint*, [46 HASTINGS L.J. 403, 453 \(1995\)](#); John J. Smith, *Science, Politics, and Policy: The Tacrine Debate*, 47 *FOOD & DRUG L.J.* 511, 530-31 (1992) (criticizing the impact of interest group pressure on FDA reviews of drugs for AIDS and Alzheimer’s disease, and concluding that “the role of political advocacy by patients and their supporters must be limited to the formulation of general new drug policy, and not allowed to become a deciding factor in decisions on individual drugs”); Lois K. Perrin, *Note, The Catch-22 for Persons with AIDS: To Have or Not to Have Easy Access to Experimental Therapies and Early Approval for New Drugs*, [69 S. CAL. L. REV. 105, 125-36 \(1995\)](#) (describing FDA responses to pressure from AIDS activists); Annaliese Smith, *Comment, Marijuana as a Schedule I Substance: Political Ploy or Accepted Science?*, [40 SANTA CLARA L. REV. 1137, 1154-64 \(2000\)](#).

<sup>142</sup> Seidenfeld, Mark Seidenfeld, *A Civic Republican Justification for the Bureaucratic State*, 105 *HARV. L. REV.* 1511 (1992)

<sup>324</sup> See generally Glen Staszewski, *Reason-Giving and Accountability*, [93 MINN. L. REV. 1253, 1279-84 \(2009\)](#) (providing a summary of arguments in favor of reason-giving); see also Martin M. Shapiro, *The Giving Reasons Requirement*, 1992 *U. Chi. Legal F.* 179, 180 (1992) (reason-giving

Some may argue that my legitimacy concerns are misplaced. The courts that heard the challenges in the reproductive drug cases, and scholars such as Lars Noah, suggest that political considerations should have no role in FDA judgment.<sup>143</sup>

Others, including then law professor Elena Kagan, suggest that such political reactions—at least in cases where values rather than science appear to be decisive in determining what constitutes a good—is desirable.<sup>144</sup> It reflects responsiveness to the democratic system—what good is voting if no administrative change comes from it?

[Discuss Kathryn Watts work. Watts argues that “agencies today tend to sweep political influences under the rug even when such influences offer the most rational explanation for the action...” She “argues for expanding current conceptions of arbitrary and capricious review beyond a singular technocratic focus so that credit would also be awarded to certain political influences that an agency transparently discloses and relies upon in its rulemaking record.” 119 *Yale L.J.* 2-85 (2009). More recently, she criticizes the “pervasive response [from] both inside and outside the courts...which simplistically views presidential influence as ‘bad’ and technocratic decision-making as ‘good.’ In narrowly focusing on the negative aspects of presidential control, expertise forcing overlooks key benefits that flow from presidential control — namely, political accountability and regulatory coherence. It also ignores the fact that presidential control is here to stay. ... [She] provide[s] a roadmap for how a wide range of non-constitutional administrative law doctrines can be coordinated to enhance the positive attributes and restrain the negative attributes of presidential control. It identifies three relevant doctrinal categories: statutorily facing rules; transparency-enhancing mechanisms; and process-forcing rules.” 114 *Mich. L. Rev.* 683-745 (2016).] \*\*\*\*\*

Whatever one’s position on that debate, however, our reality is a world where the FDA behaves politically. In such a world, decisions based on politics, values, or even indirect or third party considerations should receive a full airing. Just as members of Congress refused to confirm Clinton’s nominee as FDA Commissioner until she clarified her position on RU486, so too should her Bush predecessor have made his normative position on the drug clear.<sup>145</sup> If the FDA could explicitly avow an interest in preserving fetal development or limit racism,

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requirements improve the decisions made by administrators and enhance democratic influences); Cass R. Sunstein, *Naked Preferences and the Constitution*, [84 COLUM. L. REV. 1689, 1695 \(1984\)](#) (explaining that a reasoned decisionmaking requirement helps reduce official self-dealing and "naked preferences" for one group over another).

<sup>143</sup> See *supra*. 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.

<sup>144</sup>

<sup>145</sup> See *supra* note \_\_\_

even as unquantifiable benefits,<sup>146</sup> stakeholders could more effectively participate and influence the decisionmaking process and courts could engage in more meaningful review.

### 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.<sup>325</sup> 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 for some, moral, concerns.<sup>147</sup> Evidence existed to refute those claims.<sup>148</sup> 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: “men have even more power than they did before.”<sup>149</sup> 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

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<sup>146</sup> Cass R. Sunstein, *The Limits of Quantification*, 102 CALIF. L. REV. 1369 (2014)

<sup>325</sup> 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).

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<sup>148</sup> 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.

<sup>149</sup> Annie Potts, et al., *The Downside of Viagra: Women's Experiences and Concerns* 25 SOC. HEALTH & ILLNESS 697 (2003) (FP7, 48).



### 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.<sup>150</sup> 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 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.<sup>151</sup>

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.<sup>152</sup> 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.<sup>153</sup> But ex post regulation can under-deter because of cognitive biases—individuals discount future harms, including punishment and penalties.<sup>154</sup> It might also fail to compensate because of judgment proof defendants or other issues, which Galle refers to liquidity problems.<sup>155</sup>

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

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<sup>150</sup> Sunstein, *Health-Health Tradeoffs*, supra note \_\_, 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.

<sup>151</sup> Brian Galle, *In Praise of Ex Ante Regulation*, 68 VAND. L. REV. 1715 (2015).

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<sup>153</sup> Brief explanation of Galle's marginal analysis.

<sup>154</sup> Galle, supra note at 1721 (noting that "myopic" failure to take into account future harms or costs is far too common).

<sup>155</sup> *Id.* at 1738-43.

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 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.<sup>156</sup> 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.<sup>157</sup> 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.<sup>158</sup> 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.<sup>133</sup> 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 question, and they must not be counted more than once in the analyses that accompany more than one rule.”<sup>159</sup>

Nonetheless, even if we figure out where to draw the line, some may argue that expanding the FDA’s reach to include value judgments will harm liberty interests. But to my mind, the liberty interests cut in both directions. The FDA,

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<sup>156</sup> Admittedly, in many of these nations, the review is linked to nationalized medical systems. See NHS (UK), Patented Medicine Prices Review Board (PMPRB) (Canada); Suzanne Elvidge, *UK Government to Tackle High Drug Prices*, THE PHARMACEUTICAL JOURNAL, (Sep 20, 2016), <http://www.pharmaceutical-journal.com/news-and-analysis/news/uk-government-to-tackle-high-drug-prices/20201736.article>

<sup>157</sup> *For Want of a Nail*, WIKIPEDIA (last edited June 29, 2018) [https://en.wikipedia.org/wiki/For\\_Want\\_of\\_a\\_Nail#Historical\\_references](https://en.wikipedia.org/wiki/For_Want_of_a_Nail#Historical_references)

<sup>133</sup> 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.” S 746, § 621(11)(A)-(B), 106th Cong, 1st Sess (Mar 25, 1999). In *Am. Trucking v. Whitman*, Congress mandated considering “all identifiable effects.”

<sup>159</sup> Cass R. Sunstein, 36 Questions n. 92

like other agencies, will regulate based on values. It would be foolhardy to try and “suppress” value based instincts “out of the administrative process.”<sup>160</sup> It better respects liberty interests to engage with this kind of reasoning openly and frankly.

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.”<sup>161</sup> 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. However, the statute allows the FDA to obtain expertise as required, a feature it demonstrates regularly in the antibiotic resistance context. The FDA works collaboratively with several agencies and advisory groups in making its decisions. Although creating advisory committees are limited under the Federal Advisory Committee Act of 1972,<sup>162</sup> in the FDA context, the Secretary appears to have broad discretion to “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.”<sup>163</sup> She also has the ability to contract for expert review and is required to collaborate with other agencies on many issues.<sup>164</sup><sup>165</sup> Although the Secretary is more constrained with respect to whom she can appoint to some committees,<sup>166</sup> 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.”<sup>167</sup> Similar panels exist for classifying devices, for example, as needing pre-market approval.<sup>168</sup> The Secretary has discretion to appoint members with appropriate qualifications, including those “qualified by training and experience

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<sup>160</sup> David Arkush, *Democracy and Administrative Legitimacy*, 47 WAKE FOREST LAW REVIEW (2012) at 620.

<sup>161</sup> 138 Cong Rec 3859.

<sup>162</sup> CITE\*\*\*

<sup>163</sup> Federal Food, Drug and Cosmetic Act, 21 U.S.C. 394; §379d-1.

<sup>164</sup> *Id.* at §397. Contracts for expert review

<sup>165</sup> *Id.* at 355e(b)(4) (enforcement); *Id.* at §356c (decrease in lifesaving drugs; collaboration with DOJ).

<sup>166</sup> But the manufacturing requirements committee has 9 members and is more restrictive. Federal Food, Drug and Cosmetic Act, 21 U.S.C. 460

<sup>167</sup> *Id.* at 355(n)

<sup>168</sup> *Id.* at 360c(b)

to evaluate the safety and effectiveness of the drugs.”<sup>169</sup> <sup>170</sup> 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.”<sup>171</sup> The “FDA generally follows an advisory committee's recommendation, but is not bound to do so.”<sup>172</sup>

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.<sup>173</sup> The Secretary must also act “through” the committee in some cases.<sup>174</sup> The Secretary may also convene meetings to review safety concerns and the risk mitigation strategy involving a drug.<sup>175</sup>

The FDA also takes input from other entities in reviewing communication and advertising. The Advisory Committee on Risk Communication to “advise the Commissioner on methods to effectively communicate risks associated with the products regulated by the Food and Drug Administration.”<sup>176</sup> The Secretary has latitude to determine who is appointed to the committee. She also has the authority to go beyond the committee.<sup>177</sup> 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.”<sup>178</sup> 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.<sup>179</sup>

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<sup>169</sup> Id.

<sup>170</sup> 21 CFR § 314.50(c)(1).

<sup>171</sup> Pub. L. 114–198, title I, §106(a), July 22, 2016, 130 Stat. 702

<sup>172</sup> *Human Drug Advisory Committees*, U.S. FOOD AND DRUG ADMINISTRATION, FDA.GOV, (last updated Oct. 5, 2017), <http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/>

<sup>173</sup> Federal Food, Drug and Cosmetic Act, 21 U.S.C. 355(k)

<sup>174</sup> Id. at §355–1(e).

<sup>175</sup> Id. at 355-1 (h)(5)

<sup>176</sup> Id. at §360bbb–6

<sup>177</sup> Pub. L. 111–148, title III, §3507, Mar. 23, 2010, 124 Stat. 530, provided that:

<sup>178</sup> 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.” 360bbb–5. Critical Path Public-Private Partnerships

<sup>179</sup> JONATHAN BAERT WIENER & JOHN D. GRAHAM, *RESOLVING RISK TRADEOFFS* (1995) at 251, for example, Suggest that OIRA develop greater expertise in these kind of risk assessments. Beyond that, they suggest a 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."

#### 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 action, states are generally preempted from counteracting the FDA.<sup>180</sup> The Supreme Court has also weighed in on the question.<sup>181</sup>

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.<sup>182</sup> 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' puritan-minded, "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.<sup>183</sup>

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. 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. Similarly, if a drug were introduced to cure deafness, the FDA might recognize, but should not take into account debates on whether deafness is normal variation as some members of the deaf community have argued.<sup>184</sup> 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 the exact rule that should be followed in such cases is beyond the scope of this Article.

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<sup>180</sup> See Epstein recent article.

<sup>181</sup> Wyeth

<sup>182</sup> \*\*\*\*\* DICUSS FURTHER: Patricia J. Zettler, *Pharmaceutical Federalism*, 92 *Ind. L.J.* 845 (2017); Diana R. H. Winters, *The Benefits of Regulatory Friction in Shaping Policy*, 71 *FOOD & DRUG L.J.* 228 (2016); Lars Noah, *State Affronts to Federal Primacy in the Licensure of Pharmaceutical Products*, 2016 *MICH. ST. L. REV.* 1 (2016).

<sup>183</sup> Catherine Sharkey, n. 85.

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#### IV. STATUTORY 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.

##### A. *FDA Actions and Their Reach*

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.”<sup>185</sup>

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,<sup>186</sup> or even condition approval on the adoption of certain REMS, that might require drugs to be distributed by physicians with special training in certain facilities.<sup>187</sup> Although the regulations have rendered the statutory language more specific, as written, the law allows for some leeway.

##### 1. Approval

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<sup>185</sup> Though given recent First Amendment jurisprudence, more such limits might exist. \*\*\*See, e.g., . I cannot discuss this jurisprudence in detail, confining my comments here to the organic statute.

<sup>186</sup> [62 Fed. Reg. 8961, 8967 \(1997\)](#). See also import regulations *supra*.

<sup>187</sup> It is questionable whether the FDA had this authority until 2007. See [Washington 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 (1997); However, 2007 statutory amendments have confirmed this authority. 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, 440 (2009)

CFR: Code of Federal Regulations ; FDA.GOV, (April 1, 2017) <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcr/CFRSearch.cfm?CFRPart=314&showFR=1&subpartNode=21:5.0.1.1.4.8>

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...”<sup>188</sup>

The statute does not clearly define the term “safe.” Merriam Webster tells us that safe means “free from harm or risk.”<sup>189</sup> 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 results 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.

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 from or reduction of... fees... in the interest of public health.”<sup>190</sup> 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.<sup>191</sup>

The term public health, however, is notably 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.”<sup>192</sup> “Community health,” “preventive medicine,” “social science,” are all terms susceptible to broad interpretation. Similarly, in *Whitman v. American Trucking*, Justice Breyer endorsed a broad approach, opining that reducing income by regulation posed a “public health” risk.<sup>165</sup>

The use of the broad term “public health” when it comes to new drug (and device) applications is notable as not all applications obtain this kind of treatment. Animal drugs, in particular, only merit a reduction or waiver if they pertain to a minor use or minor species indication.<sup>193</sup>

A clue as to some safety and public health considerations might be gleaned from section 360n of the statute that sets out a 60 day limit for review of certain

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<sup>188</sup> Federal Food, Drug and Cosmetic Act, 21 U.S.C. 355(d)

<sup>189</sup> *Definition of “Safe”*, MERRIAM-WEBSTER DICTIONARY, (updated on July 5, 2018) available at [https://www.merriam-webster.com/dictionary/safe?utm\\_campaign=sd&utm\\_medium=serp&utm\\_source=jsonld](https://www.merriam-webster.com/dictionary/safe?utm_campaign=sd&utm_medium=serp&utm_source=jsonld).

<sup>190</sup> Federal Food, Drug and Cosmetic Act, 21 U.S.C. 379h(d). See also id. at 379j (device fees has similar provision).

<sup>191</sup> Id. at §360ii (“Program of control

(a) Establishment 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. ; Emergency use of devices: “(C) a determination by the Secretary that there is a public health emergency, or a significant potential for a public health emergency, that affects, or has a significant potential to affect, national security or the health and security of United States citizens living abroad, and that involves a biological, chemical, radiological, or nuclear agent or agents, or a disease or condition that may be attributable to such agent or agents;

<sup>192</sup> *Definition of “Public Health”*, MERRIAM-WEBSTER DICTIONARY, (updated July 5, 2018) available at <https://www.merriam-webster.com/dictionary/public%20health>.

<sup>165</sup> *American Trucking*, 531 US at 495.

<sup>193</sup> Federal Food, Drug and Cosmetic Act, 21 U.S.C. §§ 360b(a)(1)(C), 360ccc (2006).

drugs. Although separate from the fee setting process, the purpose of this section is also to incentivize speedy production of drugs designed to treat “tropical” public health hazards,<sup>194</sup> and lists particular diseases like Zika in that number. It also includes “[a]ny other infectious disease for which there is no significant market in developed nations and that disproportionately affects poor and marginalized populations, designated by order of the Secretary.”<sup>195</sup> Poverty and marginalization have long been considered a public health concern.<sup>196 197</sup>

Another clue as to the factors that might go into a public health or safety determination can be gleaned from 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,” such a strategy must be submitted. In making such a determination, the Secretary shall consider...factors” that range beyond expected physiological effects of the drug, 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.”

The risk mitigation strategy might require medication guides, patient package inserts, or communication plans to the relevant providers. Again, the plight of the marginalized must be taken into account. Determinations must consider “patients who have difficulty accessing health care (such as patients in rural or medically underserved areas).”<sup>198</sup>

Read in context, then, the broad terms “safety” and “public health” should not be treated as cabined to the direct physiological effects of the drug on the recipient of the drug. Rather, they should be read consonantly with other provisions of the statute that appear in the same subchapter. These provisions specifically direct the Secretary to take into account the needs of entire populations and social and structural factors regarding marginalization and the seriousness of specific conditions. While these criteria are all health related such that the Secretary could not very plausibly consider non-health related criteria, their reach is broad.

## 2. Advertising/Labeling review

Although recent Supreme Court jurisprudence might raise doubts about the full extent of FDA power in this area,<sup>199</sup> in the statute as it is written at least, the FDA has the power to penalize “false or misleading” advertising.<sup>200</sup> It may also require information regarding “side effects, contraindications, and effectiveness” to be included in advertising or labeling. It is fair to assume that

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<sup>194</sup> Cf. *id.* at 379h(d) (discussing assessment of incentives)

<sup>195</sup> (S)

<sup>196</sup> *Id.* at 360ff – rare pediatric disease.

<sup>197</sup> Similarly, the Secretary is concerned with overall supply chain issues, and is obligated to take certain steps to prevent the “meaningful disruption in the supply of [a] drug.” *Id.* at 356c. Some of these tasks are carried out in coordination with federal and state law enforcement agencies. *Id.* at 356-1(a); Ex. Ord. No. 13588, Oct. 31, 2011, 76 F.R. 68295.

<sup>198</sup> Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 355-1(f)(2)(C)(ii) (2006).

<sup>199</sup> \*\*\*\*See *supra*

<sup>200</sup> *Id.* at § 333(g).



such information concerns narrower side effects such as physiological or chemical reactions rather than broader side effects.<sup>201</sup>

In addition to this, the FDA has the authority to prereview television advertisements in certain narrow circumstances.<sup>202</sup> “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.”<sup>203</sup> 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.” 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.”

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.” 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 consumers, experts in health literacy, representatives of racial and ethnic minorities, and experts in women's and pediatric health.”<sup>204</sup>

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,” terms that are notably broader than “safety” and “public health.” And once more, these considerations may apply to the condition of entire populations rather than to specific individuals.

### 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.”<sup>205</sup> “The term “serious risk” means a risk of a serious adverse drug experience.” In turn, “serious adverse drug experience” is

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<sup>201</sup> See Craig Konnoth, *Transparency versus Informed Consent*, Working Paper, Presentation at Annual Petrie Flom Conference, Harvard Law School, 2017.

<sup>202</sup> Describe in greater detail based on the FDAAA\*\*\*\*

<sup>203</sup> Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 353c. Prereview of television advertisements

<sup>204</sup> Pub. L. 111–148, title III, §3507, Mar. 23, 2010, 124 Stat. 530, provided that:

<sup>205</sup> P. 295

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. This appears to cabin the FDA’s 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 unreasonable risk of substantial harm to the public health.”<sup>206</sup> It also allows it to *recall* any product if there is a “substantial or imminent risk to the public health.”<sup>207 208</sup> 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, these concerns must be “substantial or imminent,” even if they are not necessarily physiologically related.

### *B. Justifying Calibration*

#### 1. Calibration

The FDA interventions I list above 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.<sup>209</sup> [Explain\*\*].

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.<sup>210</sup>

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

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<sup>206</sup> 21 USC 360h.

<sup>207</sup> 42 USCS § 262,

<sup>208</sup> 21 USC 360h(e)

<sup>209</sup> Distinction between nudging and coercion. \*\*\*

<sup>210</sup> \*\*\*

require certain labeling information.<sup>211</sup> As a general matter, though, it does not generally penalize off-label use.<sup>212</sup>

One could imagine a range of other customized approaches, although this would likely require statutory alteration. 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 discrimination, the government optimizes social value. As I explain above, ensuring that only individuals who do not already use condoms get PrEP would be optimal.<sup>213</sup> 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.<sup>214</sup>

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.<sup>215</sup> 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.

This kind of calibration is not unique to the FDCA. For example, as the Fifth Circuit's gloss on the Toxic Substances Control Act observes, the Act "provides the EPA with a list of alternative actions, but also provides those alternatives in order of how burdensome they are." Much like the FDCA, the "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." 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.'"<sup>216</sup>

## 2. Justifying Calibration

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<sup>211</sup> Barbara Evans, *supra* note.

<sup>212</sup> *Understanding Unapproved Use of Approved Drugs "Off Label,"* FDA.gov (last updated June 2, 2016), <https://www.fda.gov/ForPatients/Other/Offlabel/default.htm>. 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).

<sup>213</sup>

<sup>214</sup> Craig Konnoth, *Health Information Equity*, 165 PENN L. REV. 1317 (2017).

<sup>215</sup>

<sup>216</sup> Corrosion Fittings.

Calibration might play different roles. In the Fifth Circuit case, the EPA was required to use the “least burdensome means” to achieve a particular result.<sup>217</sup> The statutory calibration helped the court determine how burdensome a particular approach was—the court, for example, noted that an action lower down the list, such as labeling, might well have achieved the same result that banning asbestos did.<sup>218</sup>

In that case, the “least burdensome” standard meant that the court would not consider the importance of the sought after goal, or the closeness of fit between the regulation and the goal. Even a relatively minor goal, if the CBA worked out, could justify a total ban if that was the least restrictive means available; a major goal could be achieved by labeling.

But in many other situations, we do consider both importance and fit. Due process doctrine for example, reflects this sort of calibration. On first glance, the doctrine recognizes different level of scrutiny depending on the right infringed rather than the severity of the burden on the right. Fundamental rights are protected using strict scrutiny, others only by rational basis scrutiny.

However, in defending the development of the undue burden standard in reproductive rights cases, Alan Brownstein’s well known article argues that 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.<sup>219</sup> Constitutional scrutiny, in turn, looks both to the “fit” between the state’s purpose and the harm it seeks to avert—for example, the likelihood that the regulation will head off the harm—as well as the importance of the purpose. A heavier burden demands a better fit and a more important purpose.

Importantly, the Court’s approach here does not especially depend on its analysis of any particular constitutional provision. When identifying a right, the Court plumbs the constitutional text and precedent. But determinations regarding burden, if not textually unmoored, seem to be based as much on common sense as upon exegesis of precedent and doctrine. The intuition appears simple—the more extreme the government’s action, the more sure and compelling must be its goals. Thus, for example, 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.<sup>220</sup>

The statute roughly tracks, and I advocate for, exactly this sort of approach. The statute appears to roughly calibrate the severity of the intervention to the criteria I lay out in Part II. 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

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<sup>217</sup> Id.

<sup>218</sup> Id.

<sup>219</sup> Alan Brownstein, *How Rights Are Infringed: The Role of Undue Burden Analysis in Constitutional Doctrine*, 45 HASTINGS L.J. 867 (1994).

<sup>220</sup> See Casey.

recommendations about advertising, for example, the FDA is able to consider overall consumer “good and well-being.”<sup>221</sup>

This calibration makes good sense and should represent the underlying logic of the FDA’s regulation even where it has statutory authority to do more. 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 should avoid doing so for pragmatic (rather than ethical) reasons. 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.

This approve-and-study approach is usually the best one when it comes to these other side effects for several reasons.

First, 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.<sup>222</sup> 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.

Finally, the calibration has to do with legitimacy. Even if the FDA had expertise and could make sound predictions, in a world with disciplinary boundaries, any overreach would sap its legitimacy.<sup>223</sup> 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.

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<sup>221</sup> Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 353b(b) (2006).

<sup>222</sup> 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.” **See also Roscoff & Revesz, *supra*, at 1777.**

<sup>223</sup> **Boundary Work**].

Of course, the extent of the harm should also be a determining factor. Even if the FDA is uncertain or lacks expertise on an issue, a harm that is extreme may merit an extreme response. In the unlikely case that PrEP were ever linked to a sudden outbreak of antibiotic resistant STDs, then coercive action may be justified to avert such an extreme harm.

### 3. Adjusting the Process

At the same time, however, the drug approval process requires modifications to assist with calibration. Some of these adjustments are clear from the PrEP approval process. First, the process for taking into account these concerns 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. 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. Yet, they were unable to provide a list to the FDA of these recommendations.

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.

## CONCLUSION

What are some examples where systematic FDA review of non-physiological, indirect, third party harms would be valuable? Consider a few examples from Part I. 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.<sup>224</sup>

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

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integrate individual health and pharmacy records. We will be able to longitudinally track the incidence of STDs among individuals on PrEP with relative ease.<sup>225</sup>

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.

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.<sup>226</sup> Although governed by a slightly different statutory scheme,<sup>227</sup> 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.

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<sup>226</sup> [Description of ban].

<sup>227</sup> 42 USCS § 262 (Regulation of biologics).