



## THE FDA: CHALLENGES FOR A NEW CENTURY, A ROUGH ROAD AHEAD FOR WOULD-BE REFORMERS

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### INTRODUCTION

Most Americans don't think a lot about the scope, magnitude, and impacts of regulation on their lives. The FDA alone, for example, regulates products that account for more than a trillion dollars annually—25 cents of every consumer dollar, and the average cost

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(including out of pocket expenses and opportunity costs) to bring a new drug to market is now about \$2.6 billion.<sup>1</sup>

However, the reassurance that regulation provides also has costs, direct and indirect. Regulation that is wrong-headed or that merely fails to be cost-effective actually costs lives, both directly by withholding life-saving products, and also by diverting societal resources to gratuitous regulatory compliance. Therefore, the number of lives saved or other benefits derived from government regulation should always be large enough to offset the costs. The diversion of resources to comply with regulation—good, bad, or indifferent—exerts an “income effect”<sup>2</sup> that reflects the correlation between wealth and health. The poorest and most vulnerable in society disproportionately bear the costs and impacts of excess regulation, while they enjoy relatively few benefits. Although it is difficult to quantify precisely the relationship between mortality and the deprivation of income, academic studies suggest as a conservative estimate that approximately every \$7 million to \$10 million of regulatory costs will induce one additional fatality through this indirect “income effect.”<sup>3</sup> Because unnecessary deaths result from regulators “erring on the side of safety,” excessive regulation has been dubbed “statistical murder”<sup>4</sup> by John D. Graham and other risk-analysis scholars.

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<sup>1</sup> Rick Mullin, *Cost to Develop New Pharmaceutical Drug Now Exceeds 2.5B*, SCIENTIFIC AMERICAN (Nov. 24, 2014), <https://www.scientificamerican.com/article/cost-to-develop-new-pharmaceutical-drug-now-exceeds-2-5b/>.

<sup>2</sup> W. Kip Viscusi, *Risk-Risk Analysis*, 8 J. RISK & UNCERTAINTY 6, 6-7 (1994) (describing a link between wealth and risk, where the more affluent select lower levels of risk).

<sup>3</sup> See W. Kip Viscusi, *How to Value a Life* (Vand. U. Law Sch. L. & Econ., Working Paper No. 08-16, 2008), [https://papers.ssrn.com/sol3/papers.cfm?abstract\\_id=1137978##](https://papers.ssrn.com/sol3/papers.cfm?abstract_id=1137978##).

<sup>4</sup> 141 Cong. Rec. 36, 2255 (1995), <https://www.congress.gov/crec/1995/02/27/CREC-1995-02-27-house.pdf> (statement of Congressman Mica, including a quote of John Graham of Harvard, “Without sound science, we are engaging in a form of ‘statistical murder.’”).

In recent years, under administrations both Democratic and Republican, the FDA has made egregious errors in both the formulation of policy and in the evaluation of individual products that have had important consequences. Most of these missteps have been in the direction of excessive risk-aversion or heavy-handed regulation, often because regulators have gotten risk-benefit judgments wrong.

In addition, FDA officials have arbitrarily introduced various obstacles to drug testing: They have directed researchers at drug companies to begin trials at inappropriately low dosages; injudiciously limited early clinical trials only to single-dose, instead of multiple-dose, studies; demanded unnecessary, invasive procedures on patients; insisted on efficacy superior to existing drugs; and required that foreign trials be completed and the results submitted before the U.S. trials could even begin.

Sen. Charles E. Grassley (R-IA) once chided drug regulators, “The health and safety of the public must be the FDA’s first and only concern.” He is right, but, particularly when governmental pre-marketing approval of a product is required, *greater health and safety are not synonymous with more stringent regulation*. Regulatory agencies should strive to impose only the amount of regulation that is necessary and sufficient, but that’s not in their nature. The late, great economist Milton Friedman observed that to gain insight into the motivation of an individual or organization, look for the self-interest. The self-interest of federal regulators lies not in serving the public interest but in expanded responsibilities, bigger budgets and grander bureaucratic empires for themselves.

As discussed below, FDA’s transgressions are not limited to human drugs, and the impacts of those transgressions have ranged from the creation of disincentives to R&D to significant threats to public health. Because of the widespread dysfunction, malfeasance and nonfeasance that plagues today’s FDA, reforms of several kinds are needed – organizational, managerial and cultural.

## I. REGULATORS' RISK-AVERSION AND BAD JUDGMENT ARE A LETHAL COMBINATION

### A. BAD JUDGMENT AND NONFEASANCE

Bringing a new human drug to market now requires 10-15 years, and costs have skyrocketed to an average of more than \$2.5 billion<sup>5</sup> (including both out-of-pocket and opportunity costs)—largely because FDA requirements have increased the length and number of clinical trials per marketing application and their complexity.

The detrimental effects of FDA delays in approving certain new drugs, especially when they have been available in other industrialized countries, are well-documented and deserve as much attention as drugs' high costs. At times, FDA officials seem to be unable to apply simple logic and appear oblivious to the fact that their decisions can literally be a matter of life or death. Consider the following examples:

#### 1. *Pirfenidone*

One example is the sorry saga of a drug called pirfenidone,<sup>6</sup> used to treat a pulmonary disorder called idiopathic pulmonary fibrosis (IPF), which killed tens of thousands of Americans annually. The cause of the disease is unknown, and there were no drug treatments approved for it in the United States until October 2014, although pirfenidone had already been marketed in Europe (since 2011), Japan (2008), Canada (2012) and China. Pirfenidone was approved in the EU on the basis of three randomized, double-blind, placebo-

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<sup>5</sup> *Cost to Develop and Win Marketing Approval for a New Drug Is \$2.6 Billion*, TUFTS CTR. FOR THE STUDY OF DRUG DEV. NEWS (Nov. 18, 2014), [http://csdd.tufts.edu/news/complete\\_story/pr\\_tufts\\_csdd\\_2014\\_cost\\_study](http://csdd.tufts.edu/news/complete_story/pr_tufts_csdd_2014_cost_study).

<sup>6</sup> Editorial, *An \$8.3 Billion Rebuke to the FDA*, WALL ST. J. (Aug. 29, 2014), <https://www.wsj.com/articles/an-8-3-billion-rebuke-to-the-fda-1409181127>.

controlled studies, one conducted in Japan and the other two in Europe and the United States.

In spite of a recommendation for approval by an FDA advisory committee (comprised of outside experts) in 2010, agency officials opted not to approve the drug and demanded another major clinical study. The results, published in May 2014, were impressive, and the FDA finally approved the drug without fanfare in October 2014; but between 2010 and the approval, more than 150,000 patients died of IPF in the United States.<sup>7</sup>

## 2. *Pro-gabapentin*

Another bizarre example of dysfunction, if not outright nonfeasance, at the FDA was its rejection of a new formulation of a popular drug, gabapentin, for the treatment of restless leg syndrome, the uncontrollable movement or twitching of the legs caused by an imbalance in the neurotransmitter dopamine in the brain. In a 2010 complete response letter – by which the FDA informs a drug sponsor that its application for approval has been denied – the FDA expressed concern about the finding of pancreatic tumors in a rat study of the drug.

Several things are problematical about this decision to deny approval.

First, the FDA knew about similar findings in animal testing of the drug when they approved the original formulation more than a decade earlier for uncontrolled epilepsy (but rationalized that that approval was justified because of the seriousness of the condition). One must wonder, then, why regulators permitted the drugmaker to plan and perform the clinical trials for the new formulation if the

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<sup>7</sup> See generally Henry I. Miller, *Life-Saving Drugs and Deadly Delays*, N.Y. POST (Sept. 28, 2014), <https://nypost.com/2014/09/28/life-saving-drugs-and-deadly-delays/>.

agency already had scientific data on the drug's risks that would prevent its ultimate approval.

Second, rats are not little people with beady eyes and long tails. When used correctly, rodents are useful models in medical testing because in many respects their genetic, biological and behavioral characteristics closely resemble those of humans, and many symptoms of human conditions can be replicated in them. But as the American Council on Science and Health has pointed out, "Differences in physiology and anatomy between humans and mice, rats, and other species often make it difficult to apply animal results confidently and directly to human health. Animal testing should not be viewed as sufficient, in the absence of additional supporting data, to predict risk to humans."<sup>8</sup>

Third, there is no additional supporting data on gabapentin<sup>9</sup> that offers any hint that it causes tumors in humans. Large epidemiological studies have failed to find any association. For example, one performed by drug company scientists using a Kaiser Permanente Northern California health system database found: "The epidemiological data in a US cohort with up to 12 years of follow-up and a UK cohort with up to 15 years of follow-up do not support a carcinogenic effect of gabapentin use. However, the confidence

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<sup>8</sup> STAFF OF THE AM. COUNCIL ON SCI. AND HEALTH, *OF MICE AND MANDATES: ANIMAL EXPERIMENTS, HUMAN CANCER RISK, AND REGULATORY POLICIES 1* (Cindy F. Kleiman, 1997), [https://books.google.com/books?id=MwBWqFwvTR8C&printsec=frontcover&source=gbs\\_ge\\_summary\\_r&cad=0#v=onepage&q&f=false](https://books.google.com/books?id=MwBWqFwvTR8C&printsec=frontcover&source=gbs_ge_summary_r&cad=0#v=onepage&q&f=false).

<sup>9</sup> Gio. B. Gori, *Regulating Unknown Risks*, REGULATION (Spring 2010), <https://object.cato.org/sites/cato.org/files/serials/files/regulation/2010/2/regv33n1-5.pdf>.

intervals for some analyses were wide, and an important effect cannot be confidently excluded.”<sup>10</sup>

### 3. *Rotarix*

Several years ago, the FDA asked pediatricians to stop administering Rotarix, a vaccine made by GlaxoSmithKline that prevents rotavirus infection, a diarrheal illness that can cause severe dehydration. The rationale was that small amounts of DNA from a pig virus had been detected in the vaccine preparation. That might sound like a good reason for concern—except that the FDA itself confirmed that the material “has been present since the early stages of the vaccine’s development.”<sup>11</sup>

In other words, all of the studies that confirmed the safety and efficacy of the vaccine had been performed with the viral DNA present, and according to the FDA, “extensive studies, including placebo-controlled, randomized clinical studies involving tens of thousands of vaccine recipients, support the safety and effectiveness of the vaccine.”<sup>12</sup> More specifically, no safety problems emerged from the pre-approval clinical trials in 90,000 subjects or during post-marketing surveillance covering more than 69 million doses of the vaccine. The head of the agency, Margaret Hamburg, even

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<sup>10</sup> Michael C. Irizarry et al., *Risk of Cancer In Patients Exposed to Gabapentin in Two Electronic Medical Record Systems*, NIH PUBLIC ACCESS 1 (Feb. 1, 2013) (manuscript), <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3314779/pdf/nihms-362279.pdf> (on file with NYU J.L. & LIBERTY).

<sup>11</sup> U.S. FOOD & DRUG ADMIN., CONFIRMATION NO. 6859563, FTS-HHS FDA 3 (Mar. 22, 2010) (Transcript of FDA Commissioner Margaret Hamburg speaking on a conference call regarding Rotarix vaccine), <https://www.fda.gov/downloads/newsevents/publichealthfocus/ucm205815.pdf>.

<sup>12</sup> U.S. FOOD & DRUG ADMIN., ADDITIONAL INFORMATION FOR HEALTHCARE PROVIDERS AND PUBLIC HEALTH PROFESSIONALS (May 14, 2010), <https://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm205548.htm>.

announced, “We’re not taking this action on the basis of a safety concern.”<sup>13</sup> She failed to state what type of concern was the basis for the action.

Consider this as well: The virus is commonly consumed in pork products and does not cause disease in any known host, including humans and pigs. One must wonder, then, what the problem was that the FDA was trying to fix by interrupting the use of the vaccine.

The story gets better: Regulators withdrew Rotarix from the market, in part, because of the availability of an alternative vaccine, Rotateq, produced by Merck. But using a new, high-sensitivity assay, Merck soon thereafter detected DNA fragments from *two* pig viruses in its vaccine.

So, did FDA officials also take the Merck drug off the market? No—instead, they rescinded the recommended pause on administration of Rotarix, the GlaxoSmithKline drug. So, are the drugs safe or unsafe? And did the FDA make its decisions in order to protect public health, or itself? This bumbling fueled the hysteria of anti-vaccine activists, and some parents were sufficiently confused that they delayed vaccinating their children. In this way, regulators created a wholly gratuitous public health problem.<sup>14</sup>

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<sup>13</sup> Rita Rubin, *FDA: Stop Using Rotarix Until Vaccine’s Extra Virus Is Studied*, USA TODAY (Mar. 22, 2010), [http://usatoday30.usatoday.com/LIFE/usaedition/2010-03-22-fda-rotarix\\_NU.htm](http://usatoday30.usatoday.com/LIFE/usaedition/2010-03-22-fda-rotarix_NU.htm).

<sup>14</sup> See generally Jennifer Walker-Journey, *FDA Lifts Temporary Ban on Rotavirus Vaccine*, RIGHTING INJUSTICE (May 19, 2010), <http://www.rightinginjustice.com/news/2010/05/19/fda-lifts-temporary-ban-on-rotavirus-vaccine/>; Lisa Richwine, *Update 2-Pig Virus DNA Found in Merck Rotavirus Vaccine*, REUTERS (May 6, 2010), <https://www.reuters.com/article/merck-rotavirus/update-2-pig-virus-dna-found-in-merck-rotavirus-vaccine-idUSN0611320520100506>; Henry I. Miller, *FDA’s Risk Aversion is Endangering Children*, FORBES (May 7, 2010), <https://www.forbes.com/2010/05/07/fda-rotateq-rotarix-vaccine-opinions-columnists-henry-miller-safety.html#3faa450a4126>.

## II. DESTRUCTION OF AN ENTIRE INDUSTRIAL SECTOR: GENETICALLY ENGINEERED ANIMALS

After more than a decade of indolent deliberations about how to review genetically engineered food animals using techniques developed in the 1980s, in 2008 the FDA opted for the most stringent, stultifying, expensive, dilatory, regulatory approach among various possible policy choices. Over the objections of animal scientists, the FDA's Center for Veterinary Medicine chose to subject genetically engineered food animals to the same burdensome pre-market approval procedures and regulations as *veterinary drugs* such as pain relievers and anti-flea medicines.<sup>15</sup> (This goes to Milton Friedman's observation, above: Among various alternatives, regulators chose the regulatory pathway that was the most intrusive, burdensome and costly.)

The rationale was that the new DNA construct in the animal and any proteins it produces are analogous to drugs that have been injected or ingested—even though animals with identical traits introduced by techniques such as breeding or artificial insemination would not be subject to any premarket review at all.

A more apposite and far less burdensome regulatory paradigm for animals used as food would be the approach taken by another FDA unit, the Center for Food Safety and Nutrition, whose policies put the burden of ensuring the safety of foods and food ingredients on those who produce them. Its regulations prohibit the adulteration (contamination) or misbranding (mislabeling) of food – which would cause regulators to initiate compliance actions – but the agency does not inspect or evaluate every new food prior to its sale in shops,

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<sup>15</sup> See U.S. FOOD & DRUG ADMIN., REGULATION OF INTENTIONALLY ALTERED GENOMIC DNA IN ANIMALS: DRAFT GUIDANCE FOR INDUSTRY (2017) at 7, <https://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM113903.pdf>.

supermarkets, or restaurants. Rather, federal oversight relies primarily on market surveillance and post-marketing regulation, and the FDA takes action if there is an apparent problem. This approach has worked quite well over many years.

The law does require a premarketing safety review for certain food-related products judged to be higher-risk. These include most food additives—a class of ingredients that includes preservatives, emulsifiers, spices, sweeteners, and natural and synthetic flavors and colors, among others.<sup>16</sup> In general, a food additive must be pre-approved if it will become a component of or otherwise affect the characteristics of a food and if it is “not generally recognized as safe (GRAS) by qualified experts for its intended use.”<sup>17</sup> (Most new genetic constructions of food animals would consist of GRAS genetic elements moved into GRAS food animals, so the result would also be GRAS.) A specific example of the dysfunction of this approach is described below.

#### A. “AQUADVANTAGE” SALMON

In November 2015 the FDA approved a genetically engineered Atlantic salmon that grows faster but is otherwise indistinguishable from its wild cohorts. It was the first “transgenic”<sup>18</sup> food animal on the market created with the molecular techniques of genetic

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<sup>16</sup> U.S. FOOD & DRUG ADMIN., DETERMINING THE REGULATORY STATUS OF A FOOD INGREDIENT (2017), <https://www.fda.gov/Food/IngredientsPackagingLabeling/FoodAdditivesIngredients/ucm228269.htm>.

<sup>17</sup> U.S. FOOD & DRUG ADMIN., GENERALLY RECOGNIZED AS SAFE (2017), <https://www.fda.gov/Food/IngredientsPackagingLabeling/GRAS/default.htm>.

<sup>18</sup> *The Sciences Behind the Rise of Biotechnology*, WHAT IS BIOTECHNOLOGY? (last visited Oct 11, 2017), <http://www.whatisbiotechnology.org/science/transgenic>.

engineering, although thousands of other such animals have been available for research purposes or as pets.<sup>19</sup>

Ronald L. Stotish, the CEO of the company that crafted the fish, commented that its approval “is a game-changer that brings healthy and nutritious food to consumers in an environmentally responsible manner without damaging the ocean and other marine habitats.”<sup>20</sup>

It was certainly a game-changer, but not quite in the way that he implied. The genetic changes made to the fish—the addition to the genome of a growth hormone gene from the Chinook salmon and a regulatory DNA sequence from the ocean pout—are minor and confer no detectable difference in its appearance, ultimate size, taste or nutritional value; the AquAdvantage just grows to maturity about twice as fast and requires significantly less food to reach maturity, tremendous economic advantages to those farming the fish in a closed water system.

The availability of such a salmon will be a boon to consumers seeking low-fat and affordable options for sources of high-quality protein, especially in the face of food price inflation,<sup>21</sup> the obesity epidemic, and given that supplies of many varieties of wild Atlantic and Pacific salmon are being depleted. However, the length and politicization of the review of this poor fish, which floundered in regulatory limbo for an astonishing *two decades*, has virtually destroyed an entire once-promising sector of biotechnology: the use

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<sup>19</sup> GLOFISH, <https://www.glofish.com> (last visited Oct. 12, 2017).

<sup>20</sup> Press Release, AquaBounty Technologies, Inc., FDA Approves AquAdvantage Salmon (Nov. 19, 2015), <http://www.prnewswire.com/news-releases/fda-approves-aquadvantage-salmon-300181839.html>.

<sup>21</sup> Tony C. Dreibus et al., *Food Prices Surge as Drought Exacts a High Toll on Crops*, WALL STREET J. (Mar. 18, 2014), [https://www.wsj.com/articles/food-prices-surge-as-drought-exacts-a-high-toll-on-crops-1395100259?mod=djemITP\\_h&mg=reno64-wsj&tesla=y](https://www.wsj.com/articles/food-prices-surge-as-drought-exacts-a-high-toll-on-crops-1395100259?mod=djemITP_h&mg=reno64-wsj&tesla=y).

of molecular genetic engineering techniques to produce improved food animals. This fish story illustrates much of what is wrong with federal regulation and offers a deplorable example of the lack of accountability when regulators fail to perform adequately.

It took the FDA more than a decade just to decide *how* they would regulate the AquAdvantage salmon. Characteristically, they decided on the most onerous pathway, treating the new construct in genetically engineered animals as though it were a veterinary drug, similar to a flea medicine or pain reliever. After several years of deliberation, regulators concluded as early as 2012 that the “AquAdvantage salmon is as safe to eat as any non-genetically engineered (GE) Atlantic salmon, and also as nutritious.”<sup>22</sup> And because the fish will all be sterile females and farmed inland, there is negligible possibility of any sort of genetic contamination of the gene pool or other environmental effects. (Even in a worst-case scenario, these coddled, farmed fish would be maladapted to compete in the wild.)

The FDA finally approved the salmon for sale in November 2015, some 22 *years* after the first submissions from the sponsor, AquaBounty. To put that absurdly lengthy review into perspective, Dr. Amanda Maxham<sup>23</sup> compiled this short list of innovative consumer products that were introduced—essentially with no regulatory delay—at the same time that AquaBounty applied for FDA approval of the AquAdvantage salmon: Nokia 9000 cell phone (which weighed almost a pound and had a black and

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<sup>22</sup> Press Release, U.S. Food & Drug Admin., FDA Has Determined That the AquAdvantage Salmon is as Safe to Eat as Non-GE Salmon (Nov. 19, 2017), <https://www.fda.gov/forconsumers/consumerupdates/ucm472487.htm>.

<sup>23</sup> Amanda Maxham, AYN RAND INST., <https://ari.aynrand.org/experts/amanda-maxham> (last visited Oct. 12, 2017).

white screen), the 28.8k dial-up modem, Amazon.com and ebay.com, Internet Explorer, the original SONY PlayStation, and the DVD.<sup>24</sup>

I would offer several salient points about the AquAdvantage fiasco. First, as discussed above, the FDA “new animal drug” model was inappropriate from the start, but if an animal drug review was going to be performed, it should have taken closer to 22 weeks than 22 years. I say that from the vantage point of someone with significant, relevant experience – viz., as the FDA reviewer of the first biopharmaceuticals in the early 1980s and as the head of the FDA’s Office of Biotechnology from 1989-1993. My team’s evaluation and approval in 1982 of the very first biopharmaceuticals, two human insulins synthesized in bacteria, was completed in five months.<sup>25</sup> It is no secret that the record of the FDA’s Center for Veterinary Medicine (CVM) on genetically engineered drugs is less than sterling. During the 1980s, CVM took *nine* years to approve bovine growth hormone (aka bovine somatotropin), a protein that increases the milk output of dairy cows, while the approval of the human equivalent, human growth hormone (for children with growth hormone deficiency), had previously been granted in 18 months.

#### B. GENETICALLY ENGINEERED MOSQUITOS

A delay in the availability of cheaper, high-quality salmon isn’t the end of the world, of course, but the FDA has also unnecessarily and inexplicably delayed small-scale field trials of mosquitoes genetically engineered to control disease-causing

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<sup>24</sup> Amanda Maxham, *Biotech Salmon Freed After 20 Years*, AYN RAND INST. (Nov. 23, 2015), <https://ari.aynrand.org/blog/2015/11/23/biotech-salmon-freed-after-20-years>.

<sup>25</sup> Lawrence K. Altman, *A New Insulin Given Approval for Use in U.S.*, N.Y. TIMES (Oct. 30, 1982), <http://www.nytimes.com/1982/10/30/us/a-new-insulin-given-approval-for-use-in-us.html>.

mosquitoes. The mosquitoes to be released are males (which do not bite) engineered to contain a specially constructed gene which, after they mate in the wild, kills their offspring. The mosquitoes have been extensively tested in a half-dozen other countries and are approved for commercial use in Brazil.

Zika virus infections, which during the past two years have swept through South and Central America and the Caribbean, are typically mild and often go undetected, but infection can cause severe birth defects early in pregnancy and subtler ones later. It can also cause a progressive, usually temporary, paralysis called Guillain-Barré syndrome. There have been tens of thousands of cases of Zika infection in U.S. territories (mostly in Puerto Rico) and more than 5,000 confirmed cases in the continental United States. Women are increasingly terrified of having babies with severe birth defects, and public health officials are worried about the prospect of enormous humanitarian and financial costs, especially in the aftermath of flooding from recent hurricanes.

Vaccines would be an effective means of prevention, but they are years—probably many years—away from commercialization, and although there is some promise in repurposing old drugs to treat Zika infections,<sup>26</sup> control of the mosquito vectors seems to be the best short-term approach. Easier said than done, however. “*Aedes aegypti*, the principal mosquito species that transmits the Zika, dengue, and chikungunya viruses, has a number of breeding and behavioral quirks that make it extremely difficult to control,” according to the World Health Organization.<sup>27</sup> Moreover, the comprehensive,

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<sup>26</sup> Ellie Kincaid, *Efforts to repurpose old drugs against Zika cast a wide net*, 22 NATURE MEDICINE 824, 824 (2016).

<sup>27</sup> *Mosquito control: can it stop Zika at source?*, WORLD HEALTH ORG., <http://www.who.int/emergencies/zika-virus/articles/mosquito-control/en/> (last visited Oct. 25, 2017).

integrated programs that could control all stages of mosquito growth are expensive and not widely available, while short-term efforts such as fogging with chemical insecticides do not work well for *Aedes aegypti*. The failure of current control programs for this species is obvious from the increasing number of cases worldwide not only of Zika virus but also of the dengue fever and chikungunya viruses, which are transmitted by the same mosquito.<sup>28</sup>

In light of the threat of Zika, chikungunya and dengue fever viruses, the WHO Vector Control Advisory Group has evaluated and recommended further development of several biological control techniques.<sup>29</sup> U.S. regulatory agencies have received requests for permission to conduct field testing of two of the most promising control techniques, both of which rely on modifying the mosquitoes in various ways to reduce the Zika threat. One of these, created by the British company Oxitec (a subsidiary of U.S.-based Intrexon), relies on a precise and predictable genetic engineering method to make a small change in the mosquitoes' genome. The result is a self-destructing, genetically-engineered mosquito that is dependent on a specific chemical to survive. Without it, they die, and when males that had been fed this chemical to keep them alive long enough to reproduce are released into the wild, their offspring inherit the mutation and die before reaching maturity. That results in a marked reduction in the mosquito population.

Because these engineered mosquitoes contain a lethal mutation and, in any case, male mosquitoes don't bite, they present

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<sup>28</sup> *Where Has Chikungunya Virus Been Found?*, U.S. CTRS. FOR DISEASE CONTROL & PREVENTION, <https://www.cdc.gov/chikungunya/geo/> (last visited Oct. 25, 2017); WORLD HEALTH ORG., *Factsheet Chikungunya*, PAN AM. HEALTH ORG., [http://www.paho.org/hq/index.php?option=com\\_content&view=article&id=8303&Itemid=40023&lang=en](http://www.paho.org/hq/index.php?option=com_content&view=article&id=8303&Itemid=40023&lang=en) (last visited Oct. 25, 2017).

<sup>29</sup> Press Release, World Health Org., Mosquito (vector) control emergency response and preparedness for Zika virus (Mar. 18, 2017), [http://www.who.int/neglected\\_diseases/news/mosquito\\_vector\\_control\\_response/en/](http://www.who.int/neglected_diseases/news/mosquito_vector_control_response/en/).

no health risk, and because their progeny die before they can reproduce, no genetically engineered mosquitoes should persist in the environment.

This approach has been successfully tested in Malaysia, Brazil, Panama and the Cayman Islands, with greater than 90% suppression of the wild population of *Aedes aegypti* mosquitoes. Brazil's national biosafety commission has authorized commercialization of the genetically-engineered mosquito and its national health agency has indicated that it will grant a special registration.

FDA took an unconscionable five years to grant permission for small-scale field testing of the Oxitec mosquito. Coincident with mounting pressure from the growing Zika threat and the consequent need to control *Aedes aegypti*, in October 2016 the FDA finally approved a field trial at a single site in the Florida Keys, some 160 miles from the Zika outbreak in Miami. In contrast, under the authority of the Federal Insecticide, Fungicide, Rodenticide Act, EPA rapidly approved the initial mosquito field trial of bacteria-infected biocontrol mosquitoes in 2013 and subsequent amendments that expanded the trials.<sup>30</sup> EPA approved them for commercial use in November 2017.

One of the challenges in the FDA's review of the Oxitec mosquito was the regulators' lack of knowledge and experience. USDA had long been the agency that managed biocontrol agents, most notably the innovative sterile screw-worm fly, which was successfully developed by USDA more than 70 years ago to eradicate a devastating agricultural pest. It is noteworthy that the scientific, agricultural and regulatory communities have more than half a century of experience with similar products—with no known

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<sup>30</sup> See Katie Pratt, *UK Collaboration Receives EPA Approval to Test Biological Control of Mosquitoes*, UKAGNEWS (Oct. 14, 2013), <http://news.ca.uky.edu/article/uk-collaboration-receives-epa-approval-test-biological-control-mosquitoes>.

problems and many significant successes. The only novel thing about the Oxitec mosquito is that its debility is conferred by an elegant molecular biological modification rather than irradiation—which makes the process more precise and predictable and arguably safer.

In spite of its specific legal authority and technical expertise for overseeing field trials and commercialization of animals, including genetically engineered insects—and also the fact that it is the EPA that has statutory oversight of insecticides—USDA ceded its authority for genetically-engineered animals to the FDA, apparently as a result of a combination of factors, including budgetary concerns and antagonism to genetic engineering among some senior USDA officials.

As discussed above, the FDA regulated the genetic material introduced into the Oxitec mosquito as a “new animal drug,” according to the rationale that introducing DNA into the genome of the mosquitoes is analogous to dosing them with a drug. Thus, in order to be marketed, the genetic material, like other “drugs,” must be shown to be *safe and effective for the animal*.

That presented a bizarre and possibly insoluble regulatory conundrum, because in order to grant commercial approval to the Oxitec product, the FDA would need to employ logic that only a bureaucrat could love: Regulators would have had to somehow conclude that the genetic material that causes a male mosquito to self-destruct after producing defective offspring is *safe and effective for the mosquito*. Facing the prospect of lawsuits blocking an ultimate approval of the genetically engineered mosquitoes, on January 18, 2017, more than six years after beginning the review of the Oxitec mosquitoes, the FDA published for public comment its “understanding that mosquito-related products intended to function as pesticides by preventing, destroying, repelling, or mitigating mosquitoes for population control purposes are not ‘drugs’ under the FD&C Act, and, when the guidance is finalized, will be regulated by EPA under FIFRA, the pesticide statute. Under the draft guidance, FDA would continue to have jurisdiction over mosquito-related

products that meet the FD&C Act drug definition, such as those intended to prevent, treat, or cure a disease.”<sup>31</sup>

One wonders what sort of “mosquito-related products” they have in mind – antidepressants or pain-relievers for mosquitoes?

### C. GENETICALLY ENGINEERED FOODS

Regulatory incentives and disincentives are potent. The vastly inflated development costs caused by over-regulation (at not only the FDA but also USDA and EPA) are the primary reason that more than 99 percent of genetically engineered crops that are being cultivated are commodity crops grown at huge scale – corn, cotton, canola, soy, alfalfa, and sugar beets.<sup>32</sup> Hawaiian papaya is one of the few examples of significant acreage currently devoted to a genetically engineered “specialty crop,” a category that includes fruits, nuts and vegetables.

The majority of American genetic engineering’s ingenuity in the agricultural sector remains sequestered in laboratories and never progresses even to field trials, let alone commercialization. Unrealized innovations in the food-animal sector include pigs and chickens that are resistant to devastating viral diseases and excrete less toxic manure, pigs with leaner muscles, and “polled” livestock (which lack horns in species that normally have horns, obviating the painful removal of horns by mechanical means).

Currently, the FDA operates a “voluntary” consultation program for genetically engineered foods whereby the developer provides the

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<sup>31</sup> Press Release, U.S. Food & Drug Admin., FDA Requests Comments on Documents Related to Certain Biotechnology and Mosquito-related Products (June 20, 2017), <https://www.fda.gov/animalveterinary/newsevents/cvmupdates/ucm536949.htm>.

<sup>32</sup> See INT’L SERV. FOR THE ACQUISITION OF AGRI-BIOTECH APPLICATIONS, *Global Status of Commercialized Biotech/GM Crops: 2016*, ISAAA: BRIEF, no. 52, 2016, at 3-4, <http://www.isaaa.org/resources/publications/briefs/52/executivesummary/pdf/B52-ExecSum-English.pdf>.

FDA various information about the product, but even that – which no food producer dares to flout – is gratuitous and excessive. And it is only “voluntary” in the same way that you “voluntarily” surrender your wallet when a robber points a gun at you. Companies fear that if they fail to submit to the consultation, they’ll be branded as being cavalier about the safety of their products, or be the target of retaliation by the FDA, which has extensive discretionary authority. (Other federal regulatory agencies – EPA and USDA – impose lengthy, mandatory, redundant reviews on the same products.)

The FDA has been very slow in performing those reviews, often taking years to conclude, for example, that a new apple variety that has had the level of several enzymes reduced and no longer turns brown when exposed to the air, is still an apple and is safe to eat. Virtually identical foods made with older, less precise and less predictable techniques are not routinely subject to any review, voluntary or otherwise.

In spite of hundreds of rigorous risk-assessment experiments (unnecessary and ill-advised as those were), there has been no reduction or rationalization of the regulatory burden placed on crops made by the newer techniques of genetic engineering.

### III. AN AGENCY BADLY IN NEED OF REFORM

The examples discussed above illustrate the unfortunate outcomes that can be inflicted by highly risk-averse “gatekeeper” regulatory agencies – like the FDA – that must grant an affirmative approval before a product can be legally marketed. The other examples illustrate the kind of poor judgment, illogic and incompetence that, combined with lack of accountability, can have significant impacts.

An endemic problem at federal agencies is “regulatory creep,” because, as former FDA Commissioner Frank Young used to quip, “Dogs bark, cows moo, and regulators regulate.” There are a number of ways in which the FDA has pushed the envelope of its statutory authority in ways that stifle innovation. In April 2007, the

FDA announced what amounts to a new extra-statutory criterion for marketing approval. Although the law requires that in order to be marketed, a drug must simply be shown to be *safe and effective*, in denying approval of Merck's new drug, Arcoxia, a COX-2 inhibitor for the relief of arthritis pain, the FDA said that the drug needed to be shown to have efficacy *superior* to existing drugs to merit approval. Robert Meyer, director of the FDA office that oversees arthritis drugs, claimed that, "It seems like [the committee] had concerns that, if there was just another product with the same level of risks of those out there now but no unique benefit, that . . . didn't seem to be sufficient reason to approve such a product."<sup>33</sup> But whether or not the advisory committee meant to convey that (and in any case, advisory committee recommendations are not binding), it is specious reasoning.

In fact, for a variety of reasons, having "another drug on the market" that appears from clinical trials data to be no better than alternatives may be important. First, there are important differences between drugs that act through similar mechanisms: Different COX-2 inhibitors and statins, for example, were shown long after the initial approvals to have distinct and critical advantages and disadvantages; physicians can select one over another, depending on how their patients respond.

Second, if two drugs are both effective in 40 percent of patients with a given symptom or disease, it may not be known whether they work in the same 40 percent. Thus, if the drugs are effective in different patient populations, the failure of regulators to approve the second drug could deprive a large number of patients of access to an efficacious drug. At best, practitioners would have fewer choices,

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<sup>33</sup> Press Release, Medical Marketing and Media, FDA panel rejects Merck's Arcoxia, (Apr. 17, 2007), <http://www.mmm-online.com/channel/fda-panel-rejects-merck-sarcoxia/article/24029/>.

and consumers would face higher prices because of a lack of competition.

Third, a substantial fraction of the prescribing of many drugs ends up being outside the primary indications specified in the original approval; these subsequent uses may be either approved or “off-label” indications (uses of the drug besides those listed on the official label). But if a drug is not approved for its initial indication because it is not sufficiently superior to a previously approved medicine, further testing might not be performed and other uses, therefore, never discovered.

Wyeth’s chairman and CEO Robert Essner described the implications of the requirement to show superiority this way: “If you’re the first company to get approved in a certain area and competitors can’t get on the market, the FDA is now establishing monopolies. And that’s certainly not their mandate.”<sup>34</sup> Whatever one thinks of regulation to ensure safety and efficacy, surely we should not have an FDA that aggressively discourages competition.

Another development is an increase in the kinds and amounts of “user fees” that companies must pay just to get the FDA to review their applications. These fees are nothing more than a discriminatory tax that ultimately will be passed on to patients. And they can be a significant burden to mid-size and small companies, particularly one-product startups; the fee for the review of a New Drug Application for 2016 was \$2.37 million. User fees are also a shabby attempt to fund government activities “off the books.” Congress should scrap the user fees, face up to its responsibilities, appropriate whatever funds it thinks are necessary for the FDA, and then permit the public to judge the results.

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<sup>34</sup> Christopher Bowe, *Wyeth Says Regulator Creating Monopolies*, FIN. TIMES (Nov. 4, 2007), [http://www.ft.com/cms/s/0/128305ba-8b41-11dc-95f7-0000779fd2ac.htmlft\\_site=falcon&desktop=true#axzz4tAICzPzO](http://www.ft.com/cms/s/0/128305ba-8b41-11dc-95f7-0000779fd2ac.htmlft_site=falcon&desktop=true#axzz4tAICzPzO).

As noted above, particularly when governmental pre-marketing approval of a product is required, *greater health and safety are not synonymous with more stringent regulation*. In fact, net benefit to patients often suffers because of a systematic regulatory phenomenon—the asymmetry of outcomes from so-called Type I and Type II errors. A regulator can err by permitting something bad to happen (e.g., approving a harmful product, a Type I error) or by preventing something salubrious from becoming available (e.g., not approving a beneficial product, a Type II error).

The two types of error are opposing sides of the same testing coin—too-aggressive attempts to reduce the incidence of Type I errors typically results in an increase in the incidence of Type II errors. Both outcomes are bad for the public, but the consequences for the regulator are very different. Type I errors are highly visible, causing the regulators to be attacked by the media and patient groups and to come to the attention of Congress, but Type II errors are usually nonevents and elicit little attention, let alone outrage.

The FDA's approval process for new drugs has long struggled with this Type I/Type II dichotomy. Consider, for example, the FDA's approval in 1976 of the swine flu vaccine. That approval is generally perceived to have been a Type I error because, although the vaccine was effective at preventing influenza, it manifested a major side effect that was unknown at the time of approval—532 cases of paralysis, including 32 deaths, from Guillain-Barré syndrome, a progressive (and usually temporary) muscle paralysis. The mistaken approval had immediate consequences: The developers of the product and the regulators who allowed it to be marketed were excoriated and punished in the modern-day pillories of congressional hearings, television newsmagazines, and newspaper editorials.

Regulators remember such occurrences and respond by being overly cautious thereafter, and the result is systematic delays in product approvals. Some of the more egregious examples of the detrimental effects of FDA's delays of drugs previously approved in other industrialized countries are described above. Although they

can profoundly compromise public health, Type II errors caused by a regulator's bad judgment, timidity, or anxiety seldom gain public attention. Often, only the employees of the company that makes the product, patients who are desperately awaiting a new therapy, and a few stock market analysts and investors are likely to be aware of them.

If a regulator's mistake precipitates a corporate decision to abandon a product, the cause and effect are seldom connected in the public mind. The companies themselves are loath to complain publicly about FDA misjudgments because the agency wields so much discretionary control over their ability to test and market products, current and future. As a consequence, there may be little direct evidence or data to document the lost societal benefits or the culpability of regulatory officials. Former FDA Commissioner Alexander Schmidt aptly summarized the regulator's conundrum:

In all our FDA history, we are unable to find a single instance where a Congressional committee investigated the failure of FDA to approve a new drug. But the times when hearings have been held to criticize our approval of a new drug have been so frequent that we have not been able to count them. The message to FDA staff could not be clearer.<sup>35</sup>

Since Dr. Schmidt's plaintive observation, there have been a few isolated demonstrations of congressional displeasure over delayed approvals, but regulators continue to introduce highly risk-averse policies, make decisions defensively, and tend to delay or reject new products of all sorts, from fat substitutes to vaccines, painkillers and flea medicines.

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<sup>35</sup> Walter E. Williams, *FDA: Friend or Foe? A MINORITY VIEW* (May 30, 2007), <http://econfaculty.gmu.edu/wew/articles/07/fda.html>.

If a regulator does not understand or is vaguely uneasy about a new product or technology, his instinct is to delay or interdict. At times, however, FDA's actions are capricious or inappropriately punitive. For example, instead of concentrating on getting more drugs through the pipeline to patients, the Agency has focused on the kinds of compliance actions that punish drug companies and their executives excessively, pleasing activists and congressional critics of industry but inhibiting innovation and injuring patients. In 2010, for example, the FDA rejected pixantrone for treating non-Hodgkin's lymphoma, a blood cancer that kills almost 12,000 Americans a year, not because the drug was not effective – in clinical trials it was a qualified success – but because the pivotal clinical trial was not “flawlessly executed.”<sup>36</sup> Maybe “flawless execution” should be the criterion for FDA managers to receive merit-pay bonuses.

The FDA's problems extend far beyond regulatory evaluations and approvals. In 2009, Chicago federal appellate Judge Richard Posner blasted the government for bringing a case against a salad-dressing wholesaler that had changed the labels on more than a million bottles of dressing to extend their shelf life. (These dates are often arbitrarily chosen and have little to do with the healthfulness or wholesomeness of the food.) Judge Posner found that not only was there nothing in food law about “best when purchased by” dates but that there was little likelihood of endangerment of public health. Moreover, he said, “the testimony of the FDA's employee was not just improper and inadmissible but incoherent.”

All of this is bad for public health and for inspiring confidence in the government. So, what is the remedy for the FDA miasma? For a start, it needs a new ethic, one that better balances the dangers of risk aversion against the benefits of timely approvals, and also new

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<sup>36</sup> Fernando Cabanillas, *Pixantrone: a new agent for relapsed aggressive lymphomas*, 13 THE LANCET ONCOLOGY 654, 654-56 (2012).

mechanisms to introduce accountability for misdeeds and missteps. To accomplish that, there will need to be reforms of the kind described in the next section and, given the outcome of the November 2016 elections, maybe there's a chance we'll get them.

#### IV. A SPECTRUM OF REFORMS

##### A. TRANSFORM FDA FROM A CERTIFIER OF PRODUCTS TO A CERTIFIER OF CERTIFIERS

On the basis of data submitted by regulated industry, the FDA evaluates the safety and efficacy of new drugs and medical devices, but a government monopoly over product regulation is not sacrosanct. Various agency functions have been outsourced over the years, with great success, so significant reform could be accomplished by expanding this concept.

Extra-governmental regulation of consumer products operates widely, efficiently and safely in the United States and abroad. In this country, Nationally Recognized Testing Laboratories,<sup>37</sup> the prototype of which is Underwriters' Laboratories, certify more than 20,000 categories of consumer products, many of which, such as electrical appliances and equipment, automotive parts, and fire-resistant building materials, present inherent potential hazards to life and property.

There are also strong precedents for the evaluation of clinical data by independent organizations. In a two-year pilot program (1992-1994) undertaken at the urging of the first Bush administration's Council on Competitiveness, the FDA contracted out reviews of submissions and compared the results of these evaluations to in-house analyses. The contractor was the Mitre

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<sup>37</sup> OCCUPATIONAL SAFETY & HEALTH ADMIN., *OSHA's Nationally Recognized Testing Laboratory (NRTL) Program*, U.S. DEP'T OF LABOR, <https://www.osha.gov/dts/otpc/nrtl/> (last visited Oct. 15, 2017).

Corporation, a non-profit technical consulting company. In all five of the submissions (supplements to New Drug Applications) reviewed by Mitre, the recommendations were completely congruent with the FDA's own evaluations. Moreover, the time required for the nongovernmental reviews was two to four months, and the cost ranged from \$20,000 to \$70,000 – fast and cheap compared to federal regulators.

This program serves as a reminder that the FDA has at one time or another delegated virtually every part of its review and evaluation functions – except for the final sign-off on marketing approval – to outside advisers, consultants, or other entities. Unfortunately, the FDA's outsourcing has generally been piecemeal, disorganized, and short-lived. (The Mitre pilot was not followed up.)

Recognizing that bureaucrats cannot duplicate the level and breadth of expertise that exists in academia, many foreign countries' regulatory agencies commonly use non-government experts for reviews and approvals. While the FDA uses non-government experts for its advisory committees, they are not permitted to do the all-important primary reviews. In 1996, the Energy and Commerce Committee considered legislation – cosponsored by nearly half of all House members – that would have allowed greater use of non-government experts. According to John J. Cohn, who was the majority (Republican) counsel for the FDA reform effort at the time, "The failure to establish a way for the FDA to benefit from valuable non-government expertise has deprived American patients of products used successfully in other countries and made U.S. industry less innovative and competitive."<sup>38</sup>

An often-cited example of successful nongovernmental oversight is the regulation of medical devices in the European Union,

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<sup>38</sup> Henry I. Miller, *The Case for FDA Outsourcing*, THE AMERICAN (Oct. 16, 2007), <http://www.aei.org/publication/the-case-for-fda-outsourcing/>.

where the system relies heavily on various sets of product standards and normally does not involve government agencies directly in product oversight. And under pressure to improve its performance nearly two decades ago, the FDA conducted a pilot program (which ended in 1998) that allowed private, third party review of most medical devices. Upon the termination of the successful pilot program, the FDA began to permit the review of specified medical devices by certain non-governmental "accredited persons." This approach should be expanded to drugs.

These kinds of third party, non-governmental oversight illustrate that there are attractive, proven alternatives to regulation by inefficient and expensive government agencies and suggest a new approach<sup>39</sup> that would allow nongovernmental "drug-certifying bodies" (DCBs) which could be profit-making or non-profit, to oversee new drug development. These bodies would compete with one another for hire by companies developing a new drug. The hired drug-certifying body would oversee investigation, help develop the New Drug Application (NDA), and then make an initial decision on the application. The FDA would have 90 days to approve or disapprove a DCB's drug certification, and a disapproval would be appealable to a board of experts reporting to the Secretary of Health and Human Services. A DCB recommendation for approval would be, in legal terms, a "rebuttable presumption," which means that the burden of proof to reverse the DCB's decision would be on the FDA.

This approach would create new competitive mechanisms rather than a single centralized bureaucracy to evaluate the merits of proposed drugs, but (because proposing to eliminate FDA entirely is a political non-starter, a libertarian pipe-dream) it would still

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<sup>39</sup> HENRY I. MILLER, *TO AMERICA'S HEALTH* xiv (Hoover Inst. Press 2000) (arguing for "private drug certifying bodies (DCBs) that would contract with pharmaceutical companies to oversee the testing and evaluation of their drugs and that would compete with one another.").

ultimately retain FDA approval over drug quality and safety standards and the certification of DCBs.

B. QUIS CUSTODIET IPSOS CUSTODES? (“WHO WILL WATCH THE WATCHERS?”)

In order to address the unhealthy dichotomy between Type I and Type II errors discussed above and to introduce accountability, there need to be “sticks” (as in “carrots and sticks”) to discipline FDA officials who transgress. This could be accomplished via a kind of ombudsman office which would need to have several characteristics: (1) an organizational location outside the agency, to provide arm’s length from FDA officials, including the Commissioner (the Department of Health and Human Services’ Office of Inspector General might be an appropriate location); (2) access to a wide spectrum of scientific, medical and regulatory expertise, either via a large number of members or ad hoc experts as necessary; and (3) authority to recommend disciplinary sanctions, ranging from censure to forfeited pay and bonuses, or demotion, depending on the egregiousness and impact of the error.<sup>40</sup>

The actions of the ombudsman office would redress, in part, the agency’s failure to effectively perform risk-risk analysis – in other words, its tendency to avoid approving a harmful product even at the expense of erecting huge economic barriers to R&D and to the availability of important new therapies. This innovative mechanism could help to balance the incentives and disincentives to regulators. More fundamentally, as a conservative governmental mechanism for correcting the entrenched bias toward eliminating all product risk regardless of the cost of lost benefits, it could be applied to other regulatory agencies as well.

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<sup>40</sup> The last of these would likely require congressional action to exempt such actions from Civil Service regulations. See also the discussion of the Holman Rule, below.

Some mechanisms to review the actions of government agencies already exist. There is the Congressional Review Act of 1996, which had been invoked only once in more than two decades prior to this year, but never successfully (largely because the president can veto the congressional action), as well as the review of new regulations by the Office of Information and Regulatory Activities (OIRA), a component of the Office of Management and Budget.

But as discussed in a Wall Street Journal article by Kim Strassel on January 26, the CRA has been underused and its potential impact, underestimated:

There was always intended to be consequences if agencies didn't deliver these reports," [Todd Gaziano, a legal scholar who as a congressional aide was intimately involved in drafting the CRA] tells me. "And while some Obama agencies may have been better at sending reports, others, through incompetence or spite, likely didn't." Bottom line: There are rules for which there are no reports. And if the Trump administration were now to submit those reports—for rules implemented long ago—Congress would be free to vote the regulations down.

There's more. It turns out the CRA has a expansive definition of what counts as a "rule"—and it isn't limited to those published in the Federal Register. The CRA also applies to "guidance" that agencies issue. Think the Obama administration's controversial guidance on transgender bathrooms in schools or on Title IX and campus sexual assault. It is highly unlikely agencies submitted reports to lawmakers on these actions.

"If they haven't reported it to Congress, it can now be challenged," says Paul Larkin, a senior legal research fellow at the Heritage Foundation. Mr. Larkin, also at Wednesday's meeting, told me challenges could be leveled against any rule or guidance back to 1996, when the CRA was passed.

The best part? Once Congress overrides a rule, agencies cannot reissue it in “substantially the same form” unless specifically authorized by future legislation. The CRA can keep bad regs and guidance off the books even in future Democratic administrations – a far safer approach than if the Mr. Trump simply rescinded them.<sup>41</sup>

Thus, the CRA is potential deregulatory dynamite, if used effectively. Since the beginning of the Trump administration, it has been used to roll back more than a dozen Obama-era regulations.<sup>42</sup>

But these “checks” on the power of regulators apply only to published rules, guidance documents and the like, but not to the case-by-case decision-making that causes so much mischief. There is also, of course, Congress’ Constitution-based oversight over Executive Branch agencies, but this has been weak in recent decades.

Two new pieces of legislation, which as of this writing have been passed by the House of Representatives, could be major steps forward on regulatory reform. The first is the aptly-named Regulations from the Executive in Need of Scrutiny (REINS) Act,<sup>43</sup> which would require *affirmative* congressional approval of any “significant” rule—defined as one that imposes compliance costs of more than \$100 million a year. If Congress fails to approve a rule within 70 days after its promulgation, it would be null and void. The “opt-in” nature of this legislation instead of the “opt-out” character of the Congressional Review Act would make it far more effective.

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<sup>41</sup> Kimberly A. Strassel, *A GOP Regulatory Game Changer*, WALL STREET J. (Jan. 26, 2017), <https://www.wsj.com/articles/a-gop-regulatory-game-changer-1485478085>.

<sup>42</sup> Stephen Dinan, *GOP rolled back 14 of 15 Obama rules using Congressional Review Act*, WASH. TIMES (May 15, 2017), <http://www.washingtontimes.com/news/2017/may/15/gop-rolled-back-14-of-15-obama-rules-using-congres/>.

<sup>43</sup> See, e.g., CONGRESS.GOV <https://www.congress.gov/bill/115th-congress/house-bill/26>.

The second is the resurrection of the “Holman Rule,” which empowers any member of Congress to propose an amendment to appropriations bills that would single out a government employee for salary reduction or to cut a specific program. A majority of the House and the Senate would have to approve any such amendment.

A structural change in the Department of Health and Human Services would also help to create accountability at the FDA and other public health agencies within the department. The FDA and 10 other operating divisions within the Department all effectively report directly to the Secretary,<sup>44</sup> who in most cases (continuously from 1993 through the Obama Administration, for example) has had no scientific or medical training; and in any case, no incumbent can master even the rudiments of all the programs within his domain.

Prior to the Clinton administration, the operating divisions responsible for various aspects of public health reported to the Assistant Secretary for Health, traditionally an experienced health professional who was responsible for overseeing and managing those agencies. President Clinton transformed the position into a policy office that manages...virtually nothing. The position is now advisory to the Secretary, so the agencies are largely unsupervised and unaccountable. The Department needs to have someone with line authority over the FDA and other operating divisions who can crack the whip when necessary.

### C. GENETICALLY ENGINEERED FOOD ANIMALS

The FDA should withdraw the regulation that describes its “new animal drug” approach to overseeing genetically engineered animals. Food animals should be subject instead to the GRAS/food

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<sup>44</sup> ASSISTANT SEC’Y FOR PUB. AFFAIRS, U.S. DEP’T OF HEALTH & HUMAN SERVICES, HHS ORGANIZATIONAL CHART (2017), <https://www.hhs.gov/about/agencies/orgchart/index.html>.

additive provisions of the FD&C Act, and other, non-food animals should be under the jurisdiction of other agencies more capable and willing to evaluate and approve them.

#### D. RECIPROCITY

The highly-publicized sudden 55-fold spike in the cost of the anti-parasite drug Daraprim<sup>45</sup> and the unexplained marked increase in the price of the epinephrine-delivery device Epi-Pen<sup>46</sup> last year elevated drug pricing to front-page news. The price of some new drugs is high, to be sure. In a commentary published in 2015, 118 oncologists advocated a grass-roots movement to check the escalation in the prices of new cancer drugs, which averaged more than \$100,000 per year in 2012. "There is no relief in sight because drug companies keep challenging the market with even higher prices," the doctors wrote in the journal *Mayo Clinic Proceedings*. "This raises the question of whether current pricing of cancer drugs is based on reasonable expectation of return on investment or whether it is based on what prices the market can bear."<sup>47</sup>

The physicians suggested various ways that drug costs could be controlled, but their proposed solutions were long on government involvement (read: arbitrary price controls) and short on market

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<sup>45</sup> Heather Long, *Drug that skyrocketed 5,000% hasn't come down in price*, CNN MONEY (Oct. 9, 2015), <http://money.cnn.com/2015/10/09/investing/drug-ceo-daraprim-price/>.

<sup>46</sup> James Paton & Naomi Kresge, *Why the \$600 EpiPen Costs \$69 in Britain*, CHICAGO BUSINESS (Sept. 29, 2016), <http://www.chicagobusiness.com/article/20160929/NEWS03/160929744/why-the-600-epipen-costs-69-in-britain>.

<sup>47</sup> Ayalew Tefferi et al., *In Support of a Patient-Driven Initiative and Petition to Lower the High Price of Cancer Drugs*, 90 MAYO CLINIC PROC. 996, 996-1000 (2015), <http://www.mayoclinicproceedings.org/article/S00256196%2815%29004309/pdf/2015-08/tl-tln050515.php>.

forces. We need less, not more, of the heavy hand of government involved in drug R&D, commercialization and reimbursement.

As noted above, bringing a new drug to market now requires 10-15 years, and costs have skyrocketed to an average of more than \$2.5 billion<sup>48</sup> (including both out-of-pocket and opportunity costs)—largely because FDA requirements have increased the length, number and complexity of clinical trials, the results of which comprise the basis of an application for marketing.

Sections IV.A. and IV.B., above, offer more systematic, sweeping approaches to correcting regulators' excessive risk-aversion and capriciousness, but other, less drastic reforms could be beneficial in the short-term. One would be the introduction of "reciprocity" of approvals with certain "A-list" foreign governments, so that an approval in one country would be reciprocated automatically by the others. That would make more drugs available sooner in all of the participating countries, increasing competition and putting downward pressure on prices.

Such an innovation would also help to alleviate another critical problem: The United States is experiencing shortages of certain critical pharmaceuticals,<sup>49</sup> many of which have been essential in medical practice for decades. The majority are generic injectable medications commonly used in hospitals, including analgesics, cancer drugs, anesthetics, antipsychotics for psychiatric emergencies, and electrolytes needed for patients on IV supplementation. Hospitals are scrambling to assure adequate supplies of drugs that are in short supply, or to find substitutes for them. Reciprocal

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<sup>48</sup> *Cost to Develop and Win Marketing Approval for a New Drug Is \$2.6 Billion*, *supra* note 5.

<sup>49</sup> See *Drug Shortages List: Current Drug Shortage Bulletins*, AMERICAN SOCIETY OF HEALTH-SYSTEM PHARMACISTS, <https://www.ashp.org/Drug-Shortages/Current-Shortages/Drug-Shortages-List?page=CurrentShortages> (last visited Oct. 12, 2017).

approvals would make numerous alternatives available, because drugs approved and on the market in other countries that are similar or identical to those in shortage would be available here.

Reciprocity of approvals could have been in place decades ago if only the FDA had met its long-standing commitment to pursue it through the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).<sup>50</sup> The ICH's agenda (supposedly) includes reciprocity of drug approvals among certain governments—but generations of FDA officials have resisted any such outsourcing of their responsibilities. When I asked a senior European regulator about the extent of the FDA's cooperation on this issue, she quipped, "It's like discussing the Thanksgiving dinner menu with the turkeys."

#### CONCLUSION

The FDA is often ponderous and inept, issuing flawed policies and making dubious decisions that inhibit innovation, damage the economy and cost lives. The Agency can and must be reformed. We need structural, policy and management changes that create incentives to regulate in a way that imposes the minimum burden possible. There are a number of possible approaches and remedies, ranging from radical to more conservative, that could be effective.

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<sup>50</sup> See INT'L. COUNCIL FOR HARMONISATION OF TECH. REQUIREMENTS FOR PHARM. USE, <http://www.ich.org/home.html> (last visited Oct. 12, 2017) ("The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) is unique in bringing together the regulatory authorities and pharmaceutical industry to discuss scientific and technical aspects of drug registration. . . ICH's mission is to achieve greater harmonisation worldwide to ensure that safe, effective, and high quality medicines are developed and registered in the most resource-efficient manner.").

Many could be accomplished administratively, but some would require congressional action.