Regulatory Transparency Project

Unlocking Innovation & Opportunity

Tales of Woe: How Dysfunctional Regulation Has Decimated Entire Sectors of Biotechnology

FDA and Health

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The views expressed are those of the author in his personal capacities and not in his official/professional capacities.

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Table of Contents

Introduction

"To observe government is to observe the absence of accountability," James Freeman wrote in the *Wall Street Journal*.[1] That's certainly true of unwise regulation of many innovative technologies; and modern biotechnology, also known as "genetic engineering (GE)" or "genetic modification (GM)," perhaps along with civilian applications of nuclear power, could be the poster child.

Over four decades, genetic engineering has produced monumental scientific, technological, economic, and humanitarian advances in medicine and agriculture. And yet, because of persistent over-regulation and the relentless antagonism of self-interested activists, it has realized only a fraction of its potential. Indeed, *entire sectors* of genetic engineering, some or all of which had the potential to produce the Next Big Thing in American innovation, have been decimated.

I. Biotech Regulation's Original Sin

In the early 1970s a group of scientists -- none involved in agriculture or food science -- raised concerns about hypothetical hazards that might arise from the use of the newly discovered molecular genetic modification technique (recombinant DNA technology, or "gene-splicing") that could alter the inheritable characteristics of an organism via directed changes in its DNA.[2] It greatly facilitated the transfer of genetic material (and, therefore, of traits) from one organism to another.

That led to guidelines[3] crafted and published by the U.S. National Institutes of Health (NIH) for the use of these techniques for any purpose. These "process-based" guidelines, which were applicable exclusively to the use of recombinant DNA technology, were in addition to the preexisting "product-focused" regulatory requirements of other federal agencies that had oversight of food, drugs, certain plants, pesticides, and so on.

The regulations were quite stringent. For example, without regulatory approval the "intentional release" of "recombinant organisms" into the environment, or fermentation (in contained fermenters) at volumes greater than ten liters, required explicit prior approval by the NIH and local Institutional Biosafety Committees.

No analogous, blanket restrictions existed for similar or even virtually identical plants, microorganisms, or other organisms modified by traditional techniques, such as chemical or irradiation mutagenesis or wide-cross hybridizations.[4]

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[1] Freeman, J. A New Sheriff for Parkland, Wall Street Journal, 8 February 2019. https://www.wsj.com/articles/a-new-sheriff-for-parkland-11549663545?mod=searchresults&page=1&pos=1 [accessed 4 March 2019]

[2] Hanna, K.E., editor. Institute of Medicine (US) Committee to Study Decision Making; Hanna KE, editor. Washington (DC): National Academies Press (US); 1991. https://www.ncbi.nlm.nih.gov/books/NBK234217/ [accessed 4 March 2019]

[3] National Institutes of Health, NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules, April 2016. https://osp.od.nih.gov/wp-content/uploads/2013/06/NIH_Guidelines.pdf [accessed 4 March 2019]

[4] Goodman, R, et al. Science 236 (1987), 48-54. https://execdeanagriculture.rutgers.edu/pdfs/goodman-k06.pdf [accessed 13 April 2019]

Thus, uninformed and ill-founded concerns about the risks of recombinant DNA-modified organisms in medical, agricultural, and environmental applications precipitated the regulation of recombinant organisms triggered simply by the "process," or technique, for genetic modification, rather than the "product," i.e., the characteristics of the modified organism. This was an unfortunate precedent – as was entrusting technology regulation to a research agency, the NIH -- whose legacy plagues regulation worldwide today.

The regulatory burden on the use of recombinant DNA technology was, and remains, disproportionate to its risk, and the opportunity costs of regulatory delays and expenses are formidable. According to Wendelyn Jones at DuPont Crop Protection, a survey found that "the cost of discovery, development and authorization of a new plant biotechnology trait introduced between 2008 and 2012 was $136 million. On average, about 26 percent of those costs ($35.1 million) were incurred as part of the regulatory testing and registration process."[5]

Thus, given that as of 2016, at least 120 genetically engineered seeds with new traits had been approved (in regulatory parlance, "deregulated") by USDA,[6] the public and private sectors have spent billions of dollars on complying with superfluous, redundant regulatory requirements that have priced public sector and small companies' agricultural research and development out of the marketplace.

These inflated development costs are the primary reason that more than 99% of genetically engineered crops that are cultivated today are large-scale commodity crops—corn, cotton, canola, soy, alfalfa and sugar beets. Virus-resistant Hawaiian papaya, bruise- and fungus-resistant potatoes, and non-browning apples are among the few examples of genetically engineered "specialty crops," such as fruits, nuts, and vegetables.

Early concerns from the food industry about possible food contamination led to onerous USDA restrictions on the once-promising sector of biotechnology called "biopharming," which uses genetic engineering techniques to induce crops such as corn, tomatoes, and tobacco to produce high concentrations of high-value pharmaceuticals.[7] Likewise, the once high hopes for genetically engineered "biorational" microbial pesticides and microorganisms to clean up toxic wastes are dead and gone. And not surprisingly, few companies or other entities are willing to invest in the development of badly needed genetically improved varieties of the subsistence crops grown in the developing world.

While huge, multinational agribusiness companies can bear the high regulatory costs for high-value, large-volume commodity grains, excessive regulation disproportionately affects small enterprises and, especially, public research endeavors such as those at many universities, which lack the

[5] GMO Answers, November 7, 2013. https://gmoanswers.com/experts/wendelyn-jones. [accessed 4 March 2019]
[6] Genetic Literacy Project, Which genetically engineered crops are approved in the U.S.? https://gmo.geneticliteracyproject.org/FAQ/which-genetically-engineered-crops-are-approved-in-the-us/ [accessed 4 March 2019]
[7] Miller, H.I. Down on the Biopharm. Policy Review, December 2013-January 2014. https://www.hoover.org/research/down-biopharm [accessed 4 March 2019]

necessary resources to comply with burdensome and costly regulatory requirements. Therefore, publicly-supported institutions have been put at a substantial competitive disadvantage and are seldom able to create important new varieties or to expose their students to state-of-the-art breeding programs.

The regulatory compliance costs associated with a new insect-resistant or herbicide-resistant recombinant DNA-modified variety of corn, for example, which are, as noted above, around $35 million[8], do not include the resources spent on products that are never approved; the costs borne by growers, shippers and processors associated with required segregation, traceability, and special labeling; or the opportunity costs of compliance with unnecessary regulation.

II. "New Breeding Techniques" (NBTs) in Agriculture

The history of agriculture is one of constant, incremental improvements to plants, animals, and microorganisms to improve quality, yield, and efficiency, as well as in technologies for food production, environmental protection, and sustainability.

New breeding techniques (NBTs) are new methods of genetic engineering, such as CRISPR (clustered regularly interspaced short palindromic repeats), that give scientists the ability to more precisely genetically modify crops and animals. Using NBTs, researchers can enhance or silence or insert or remove desired traits.

Although similar to other techniques for genetic improvement that have modernized agriculture, modern molecular genetic engineering, including NBTs, offers more precise and efficient ways to:

- Increase crop productivity by means of:
    - Disease and pest resistance
    - Drought resistance
    - Flood resistance
    - Adaptation to temperature variation
    - More efficient metabolic pathways
- Decrease costs of food-animal production
    - Faster, more efficient growth
    - Easier to manage, e.g., hornless cattle
- Greater farm-to-market efficiency
    - Longer shelf-life, fresher produce

[8] GMO Answers, November 7, 2013. https://gmoanswers.com/experts/wendelyn-jones. [accessed 4 March 2019]

- Improved nutrition and taste
    - Improved nutrient quality
    - Added vitamins and minerals (e.g., vitamin A and iron-fortified grains)
- Protect the environment
    - More efficient water utilization
    - Reduced inputs such as fertilizers, herbicides, and insecticides
    - Promotes no-till farming, which results in less runoff, soil erosion, and CO_2 release
    - Animals with less toxic waste products and less CO_2 production
    - Bioremediation
- Improve food processing
    - Processing enzymes such as genetically engineered chymosin to replace rennet
- Manufacture of specialized products (e.g., "biopharming")
    - Pharmaceuticals
    - Chemicals

In spite of decades of over-regulation, the contributions of molecular genetic engineering to agriculture have been prodigious. According to economists Graham Brookes and Peter Barfoot:

> economic benefits at the farm level amounting to $15.4 billion in 2015 and $167.8 billion for the 20-year period 1996-2015 (in nominal terms). These gains have been divided 49% to farmers in developed countries and 51% to farmers in developing countries. About 72% of the gains have derived from yield and production gains with the remaining 28% coming from cost savings.[9]

Genetic engineering has also led to significantly reduced negative impacts on the environment:

> GM traits have contributed to a significant reduction in the environmental impact associated with insecticide and herbicide use on the areas devoted to GM crops (Table 6). Since 1996, the use of pesticides on the GM crop area was reduced by 618.7 million kg of active ingredient (8.1% reduction), and the environmental impact associated with herbicide and insecticide use on these crops, as measured by the [Environmental Impact Quotient], fell by 18.6%.[10]

[9] Brookes, G. and Barfoot, P. (2017) GM crops: global socio-economic and environmental impacts 1996- 2015 http://www.pgeconomics.co.uk/pdf/2017globalimpactstudy.pdf. [accessed 4 March 2019]

[10] Brookes, G. and Barfoot, P. (2017) GM crops: global socio-economic and environmental impacts 1996- 2015. http://www.pgeconomics.co.uk/pdf/2017globalimpactstudy.pdf [accessed 4 March 2019]

The authors have also quantitated the environmental benefits of reduced fuel use from less frequent herbicide or insecticide applications and a reduction in the energy use in soil cultivation:

> The fuel savings associated with making fewer spray runs (relative to conventional crops) and the switch to conservation, reduced and no-till farming systems, have resulted in permanent savings in carbon dioxide emissions. In 2015, this amounted to about 2,819 million kg (arising from reduced fuel use of 1,056 million liters. Over the period 1996 to 2015 the cumulative permanent reduction in fuel use is estimated at 26,223 million kg of carbon dioxide (arising from reduced fuel use of 9,821 million liters).[11]

Finally, they cite the benefits of "'no-till" and "reduced-till" farming systems:

> These production systems have increased significantly with the adoption of GM [herbicide-tolerant] crops because the GM [herbicide-tolerant] technology has improved farmers' ability to control competing weeds, reducing the need to rely on soil cultivation and seed-bed preparation as means to getting good levels of weed control. As a result, tractor fuel use for tillage is reduced, soil quality is enhanced and levels of soil erosion cut. In turn, more carbon remains in the soil and this leads to lower [greenhouse gas] emissions.[12]

III. The Risks of Recombinant DNA and New Breeding Techniques (NBTs) in Agriculture

Recombinant DNA (r-DNA)-mediated genetic engineering involves cutting and splicing DNA with enzymes called restriction nucleases and often involves inserting a new, small segment of DNA to change or improve an organism's characteristics. Recombinant DNA and newer, even more precise techniques provide greater power, precision, and efficiency than traditional methods for plant and animal breeding, food production, environmental and other applications.

The fundamental concern underlying the basis for regulation of recombinant DNA technology in the 1970s was whether it conferred unique risks because of the combination of particular DNAs or the introduction into organisms of foreign genomic material. Numerous national and international scientific organizations have repeatedly addressed this question, and hundreds of risk-assessment experiments have been conducted, many under the aegis of the highly risk-averse European Commission. The results have led to a broad consensus that no unique or incremental risks are likely to arise from the use of the newer GE techniques, per se.

Among scientists, there is a broad and longstanding consensus that GE crops and foods are no less safe than corresponding conventionally bred crops and foods. In the nearly half a century since its

[11] Idem.
[12] Idem.

inception, not a single incidence of harm to human health or to an ecosystem attributed to a GE modification has been documented.

The U.S. National Academies of Science, Engineering and Medicine's Consensus Study Report, "Genetically Engineered Crops: Experiences and Prospects (2016)," concluded that "no differences have been found that implicate a higher risk to human health safety from these GE foods than from their non-GE counterparts." Similarly, "Overall, the committee found no conclusive evidence of cause-and-effect relationships between GE crops and environmental problems."[13]

This latest National Academies report is only the most recent in a decades-long history of scientific reports, the most definitive of which were published in 1987 and 1989. The conclusions of the former included:

- There is no evidence that unique hazards exist either in the use of [r-DNA] techniques or in the transfer of genes between unrelated organisms.
- The risks associated with the introduction of [r-DNA] engineered organisms are the same in kind as those associated with the introduction into the environment of unmodified organisms and organisms modified by other genetic techniques.

In the most comprehensive and unequivocal analysis, the 1989 U.S. National Research Council report, "Field Testing of Genetically Modified Organisms," on the risks of genetically engineered plants and microorganisms, concluded that "the same physical and biological laws govern the response of organisms modified by modern molecular and cellular methods and those produced by classical methods."[14]

But this analysis went further, emphasizing that the more modern molecular techniques are more precise, circumscribed, and predictable than other methods – in other words, if anything, likely to be *safer*:

- Crops modified by molecular and cellular methods should pose risks no different from those modified by classical genetic methods for similar traits. As the molecular methods are more specific, users of these methods will be more certain about the traits they introduce into the plants.
- Recombinant DNA methodology makes it possible to introduce pieces of DNA, consisting of either single or multiple genes, that can be defined in function and even in nucleotide sequence. With classical techniques of gene transfer, a variable number of genes can be transferred, the number depending on the mechanism of transfer; but predicting the precise

[13] National Academies, Genetic Engineering of Crops: Experience and Prospects (2016). https://www.nap.edu/catalog/23395/genetically-engineered-crops-experiences-and-prospects [accessed 4 March 2019]

[14] National Academies (1989). Field Testing Genetically Modified Organisms. https://www.nap.edu/catalog/1431/field-testing-genetically-modified-organisms-framework-for-decisions [accessed 4 March 2019]

number or the traits that have been transferred is difficult, and we cannot always predict the phenotypic expression that will result. With organisms modified by molecular methods; we are in a better, if not perfect, position to predict the phenotypic expression.

New Breeding Techniques (NBTs). In contrast to recombinant DNA technology, which most often involves adding a DNA segment, rapidly emerging new breeding techniques (NBTs) employ recently developed technologies that often simply modify or edit existing DNA. These new "genome editing" techniques include zinc finger nucleases, TALENs, CRISPR-Cas9, and CRISPR-Cas13. The use of NBTs gives researchers the ability to readily modify specific genes without having to introduce DNA from another species (not to imply that that is problematic in any way, however). NBTs can far more precisely deliver the same changes as those from traditional, unregulated technologies such as induced mutagenesis.

At the end of the Obama administration, the Food and Drug Administration (FDA) proposed lumping NBT-modified animals into the same illogical, over-regulated regime as recombinant DNA-modified ones (*vide infra*); FDA has not yet advanced this proposal under the Trump administration, although then-Commissioner Scott Gottlieb said that he favored it. USDA has said that it will not regulate NBT-modified plants, as it lacks legal authority unless the modified organisms contain genetic material from a regulated plant pest. EPA has expressed interest in expanding its scope of regulation.

IV. Regulatory Tales of Woe

Some regulators seem to be slow learners. Or, more likely, they repeatedly illustrate the late economist Milton Friedman's observation that in order to understand the motivation of an individual or organization, you need to follow the self-interest: The self-interest of regulators is to arrogate new responsibilities, get bigger budgets, command ever-larger bureaucratic empires, and avoid approving any product that could conceivably present an unforeseen, high-profile problem.

The "tales of woe" described below, which have stymied entire sectors of molecular genetic engineering in the United States, and thereby resulted in untold opportunity costs, should serve as a cautionary tale.

"Ice-minus" bacteria to prevent frost damage to crops.

Frost damage to crops is not unusual; it causes American farmers to lose billions of dollars annually. Peaches, plums, citrus and other crops are regularly threatened by frost in the Southeast, but California is also susceptible: A freeze there in January 2007 cost farmers more than $1 billion in losses of citrus, avocados and strawberries, and a 1990 freeze that caused about $800 million in damage to agriculture resulted in the layoff of 12,000 citrus industry workers, including pickers, packers, harvesters and salespeople. In 2002, lettuce prices around the country spiked after an unseasonable frost struck the Arizona and California deserts.

Technology could mitigate much of the damage, but government regulation has placed obstacles in the way of innovative solutions. Those obstacles illustrate what innovators are up against, and how flawed, unscientific public policy prevents science and technology from realizing their potential.

Currently, farmers' tools for preventing frost damage are pathetically low-tech. Methods include burning smudge pots to produce warm smoke; running wind machines to move the frigid air; and spraying water on the plants to form an insulating coat of ice. The only high-tech solution -- a clever application of biotechnology discussed below -- has been frozen out by federal regulators.

In the early 1980s, scientists in the agbiotech industry and at the University of California, Berkeley, devised an ingenious approach to limiting frost damage.

There is a harmless bacterium, *Pseudomonas syringae*, which lives on many plants, and contains an "ice nucleation" protein that promotes frost damage. These scientists, therefore, decided to produce a variant of the bacterium that lacks the ice-nucleation protein, reasoning that spraying this variant bacterium (dubbed "ice-minus") on plants might prevent frost damage by displacing the common, ice-promoting kind. Using very precise recombinant DNA techniques, the researchers removed the gene for the ice-nucleation protein and planned field tests with the ice-minus bacteria.

Then the government stepped in.

The Environmental Protection Agency (EPA) classified the innocuous ice-minus bacterium, which was to be tested in northern California on small, fenced-off plots of potatoes and strawberries, as a *pesticide*. The rationale was that because the naturally occurring, ubiquitous "ice-plus" bacterium promoted frost damage, and was, therefore, a "pest," other bacteria intended to mitigate its effects would be considered a pesticide. This is the kind of absurd, sophistic reasoning that could lead the EPA to regulate outdoor trash can lids as a pesticide because they deter or mitigate the actions of a "pest"-- namely, raccoons.

At the time, scientists inside and outside the EPA unanimously agreed that the test posed negligible risk. (I wrote the analysis submitted by the Food and Drug Administration.) No new genetic material had been added -- only a single gene whose function was well known had been deleted -- and the organism was obviously harmless. Nonetheless, the field trial was subjected to an extraordinarily long and burdensome review -- by both the NIH and EPA -- only because the organism was genetically modified with recombinant DNA techniques.

It is noteworthy that small-scale field trials using bacteria with identical traits but constructed with older, cruder techniques require no governmental review of any kind. (There are natural, ice-minus mutants of *P. syringae*, but because the gene for the ice-nucleation protein is not completely deleted, the mutation isn't permanent.) When field-tested on less than 10 acres, non-engineered bacteria and chemical pesticides are completely exempt from regulation. Moreover, there is no government

regulation at all of the vast quantities of the "ice-plus" organisms (which contain the ice-nucleation protein) that are commonly blown into the air during snowmaking at ski resorts.[15]

Although the ice-minus bacteria proved safe and effective at preventing frost damage in field trials, further research and commercialization were discouraged by the combination of onerous government regulation, the inflated expense of doing the experiments, and the prospect of huge downstream costs and stigma of pesticide registration. As a result, the product was never commercialized, and plants cultivated for food and fiber throughout the nation remain vulnerable to frost damage. We have the EPA to thank for farmers' jeopardized livelihoods, lost jobs, and inflated produce prices following winter and spring frosts.

That last point illustrates the ripple effect -- in this case the public health impact -- of such government actions. The demand for fresh fruits and vegetables is elastic, so higher prices reduce consumption, which causes consumers to get less of the antioxidant, vitamin and high-fiber benefits afforded by these products.

Biorational pesticides.

The ice-minus fiasco is not an isolated example. At around the same time, the Monsanto Company proposed a small-scale field trial that was scientifically interesting and potentially important -- control of a corn-eating insect by a harmless soil bacterium, *Pseudomonas fluorescens*, into which scientists had spliced the gene expressing an insecticidal protein from another, equally innocuous bacterium. Despite the unanimous conclusion of the EPA's external scientific advisory panel and other federal agencies (I wrote the FDA's opinion) that the risk of the field trial was negligible, the EPA denied permission. The rationale was that public opinion wasn't ready.

Two aspects of this situation are noteworthy: As was the case for the ice-minus bacteria, the field trial would not have been subject to any government regulation at all, had the researchers used an organism with identical characteristics but crafted with less precise "conventional" genetic techniques; and Monsanto's response to the rejection was to dismantle its entire research program on microbial biocontrol agents. This program could have developed biological agents to replace chemical pesticides -- an express goal of the EPA during the Clinton administration – but the EPA's heavy-handed, unscientific policies and decisions had a lasting, chilling effect on the entire sector of biocontrol R&D.

Bioremediation.

This once highly touted application of biotechnology involves supplementing a contaminated ecosystem with genetically engineered microorganisms or other organisms able to degrade and

[15] https://www.google.com/search?hl=en&tbm=isch&source=hp&biw=1151&bih=511&ei=X1kyXOdFnrHQ8Q-7hqeIBQ&q=snow-making&oq=snow-making&gs_l=img.3..35i39j0j0i30l5j0i10i30j0i30l2.542.3014..3384...0.0..1.64.652.11.....1....1..gws-wiz-img.....0..0i10.yrcbkjoVTo0#imgrc=_ [accessed 12 March 2019]

detoxify the contaminants. The goal is to reduce pollutant levels to undetectable, nontoxic, or acceptable levels.

During the 1980s microorganisms genetically engineered to feed on spilled oil were developed in various laboratories, but Draconian federal regulations discouraged their testing and commercialization and ensured that the only techniques available for responding to these disasters remain low-tech and marginally effective. They include methods such as deploying booms to contain the oil, spraying chemicals to disperse it, burning it, and spreading absorbent mats.

At the time of the catastrophic 1989 Exxon Valdez oil spill in Alaska, there were great expectations for modern biotechnology applied to bioremediation, including of oil spills. William Reilly, who headed the Environmental Protection Agency at the time of the spill, later recalled (at a lecture at Stanford University that I attended), "When I saw the full scale of the disaster in Prince William Sound in Alaska ... my first thought was, Where are the exotic new technologies, the products of genetic engineering, that can help us clean this up?"

Those "exotic new technologies" remained in laboratories but were never field tested or commercialized because, characteristically, Mr. Reilly's EPA didn't let science get in the way of policy, and erected insuperable obstacles. Its regulation focuses on any "new" organism -- strangely and unscientifically defined as one which contains combinations of DNA from unrelated sources -- that might, for example, literally eat up oil spills. For the EPA, then and now, "newness" is synonymous with risk, and because genetic engineering techniques can easily be used to create new gene combinations with DNA from disparate sources, these techniques therefore "have the greatest potential to pose risks to people or the environment," according to the agency press release that accompanied the rule.

But science says otherwise. The genetic technique employed to construct new strains is irrelevant to risk, as is the origin of a snippet of DNA that may be moved from one organism to another: What matters is its *function*. Scientific principles and common sense dictate which questions are central to risk analysis for any new organism. How hazardous is the organism you started with? Is it a harmless, ubiquitous organism found in garden soil, or one that causes illness in humans or animals? Does it harbor potent toxins? Does the genetic change merely make the organism able to degrade oil more efficiently, or does it have other effects, such as making it more resistant to antibiotics and therefore difficult to control? Instead, EPA selected an arbitrary and unscientific trigger for regulation.

Genetically engineered animals.

This biotechnology sector once offered tremendous promise but has been a disappointment, as illustrated by the relatively few genetically engineered animals that have reached the market. In research studies, animals that have been genetically engineered include cattle, pigs, chickens, goats, sheep, dogs, cats, fish, rats, and mice. Most of the rodents have been for models of human disease, or to study how genes affect health and disease.

A fascinating application is the genetically engineered Enviro-Pig™, whose feces contain 30 to 60 percent less phosphorus than traditional pigs fed the same conventional diet. This lessens the animals" impact on the environment. Other potentially important genetically engineered animals that likewise have not been commercialized include virus-resistant chicken strains that could benefit poultry breeders and also eliminate birds as a reservoir for pandemic strains of human influenza and other viruses.

A potentially revolutionary development in animal genetic engineering would be the creation of lines of pigs with organs that could be transplanted into humans[16]. This application would be life-saving for many patients on waiting lists for kidneys, livers, lungs, and hearts. (More than 100,000 people are currently on waiting lists for transplants.) It assumes greater significance than ever in view of a recent study that found a significant incidence of hypertension, diabetes and other disorders in living donors of kidneys for transplantation[17].

However, except for rodents used in research, the promise of genetically engineered animals has been nearly extinguished by the FDA, which hit the sector with a double-whammy: First, by adopting a policy that over-stepped language of the agency's enabling statute, and then by implementing the policy in a way that is unnecessarily burdensome and is so incompetent that it actually strains credulity.

Regulators over-stepping the statute in a way never intended by legislators seems to run contrary to Article I of the U.S. Constitution, which vests all legislative power in the Congress, yet it can happen because the Congress has delegated broad rulemaking authority to Executive Branch agencies. They, in turn, interpret their rules in ways that inexorably expand their mandate, budgets and bureaucratic empires.

In its 2008 "Guidance for the Regulation of Genetically Engineered Animals Containing Heritable rDNA Constructs," FDA announced that "recombinant DNA," when introduced into the DNA of an animal, is a "new animal drug" and thereby requires the animal to be reviewed as a drug under the Federal Food, Drug and Cosmetic Act.[18] Accordingly, in order to be sold, the animal must undergo government review and approval, the same as a veterinary drug like an antibiotic or pain reliever.

The 2008 guidance focuses inappropriately on the use of a single, highly precise breeding technique among the spectrum of techniques used by animal breeders -- but without identifying a demonstrable, rather than speculative, risk as the basis for imposing the high evidential standard of drug "safety and effectiveness" required by the FDA's new animal drug regulations.

There is no hint anywhere in the Food, Drug and Cosmetic Act, the FDA's primary enabling statute, that animals could be, in effect, regulated as a drug. Nor was such an interpretation necessary for

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[16] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5617878/ [accessed 13 April 2019]
[17] https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2730470 [accessed 13 April 2019]
[18] FDA. Guidance for Industry: Regulation of Genetically Engineered Animals Containing Heritable rDNA Constructs. https://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM052463.pdf [accessed 12 March 2019]

the safe sale and consumption of genetically engineered animals. A more apposite model is the way that another FDA component, the Center for Food Safety and Nutrition, regulates foods. The law places the burden of ensuring the safety of foods and food ingredients on those who produce them. It prohibits the adulteration (contamination) or misbranding (mislabeling) of food, but regulators do not inspect or evaluate all food before its sale in shops, supermarkets, or restaurants. Rather, FDA's oversight (which encompasses all food except meat, poultry, and egg products, that are regulated by the Department of Agriculture) relies on market surveillance or other post-marketing regulation, and the FDA takes action only if there is an apparent problem.

The law does require a premarketing review for certain food-related products: "Any substance that is reasonably expected to become a component of food is a food additive that is subject to premarket approval by FDA, unless the substance is generally recognized as safe (GRAS) among experts qualified by scientific training and experience to evaluate its safety under the conditions of its intended use or meets one of the other exclusions from the food additive definition in section 201(s) of the Federal Food, Drug, and Cosmetic Act (FFDCA)[19]." Food additives include preservatives, emulsifiers, spices and sweeteners, and natural and synthetic flavors or colors, among others.

GRAS is an important concept, especially in the context of genetically engineered animals. Before a new food ingredient is marketed, it is the responsibility of the producer to determine whether or not the substance is GRAS. The agency routinely reviews food additive applications for safety only when the substance in question has been determined not to be GRAS by the producer. If the producer determines that a substance is GRAS, only a notification of that decision to the FDA is necessary (which is then subject to agency review).

Another important aspect of the GRAS concept is that multiple GRAS substances that have been combined are still considered GRAS. Similarly, because adding a GRAS gene to a GRAS organism is likely to yield a GRAS outcome, a lengthy FDA premarketing review should not be necessary for genetic constructions like the genetically engineered salmon discussed below.

The story of the fast-growing AquAdvantage[R] salmon is the poster-child for bureaucrats' incompetence and bad faith. This is a farmed genetically engineered Atlantic salmon that reaches maturity 40% faster than its wild cohorts and consumes 25% less food while it grows to maturity. The genetic changes confer no detectable difference in the fish's appearance, ultimate size, taste, or nutritional value; it just grows faster and consumes less food over its lifetime. Also, because the fish are all sterile females and farmed inland in a closed system, there is negligible possibility of any sort of "genetic contamination" of the wild fish gene pool or other environmental effects[20].

More than a decade before the FDA issued its guidance in 2008, its officials had told the developer to submit a marketing approval application to FDA, but without a clear regulatory rationale or

[19] https://www.fda.gov/Food/IngredientsPackagingLabeling/FoodAdditivesIngredients/ucm228269.htm [accessed 13 April 2019]

[20] https://gmoanswers.com/nine-9-things-you-need-know-about-gmo-salmon [accessed 13 April 2019]

pathway. The FDA held up the application for approval[21] of the salmon for almost 13 years before even reaching a decision on how this fish should be reviewed. Review of the salmon as a "new animal drug" required several more years. At the end of a two-decades-long regulatory process, FDA concluded what should have been obvious long before: that no health or environmental risks or food quality concerns existed. By contrast, the FDA's approval in 1982 of the first recombinant DNA-derived pharmaceutical, human insulin produced in genetically engineered bacteria, took only five months. (I was the medical reviewer and head of the review team.)

The last obstacle to farming and selling the salmon in the United States was removed in March 2019, but thanks to various legislative obstacles thrown up by Sen. Lisa Murkowski (R-AK), it is still not in markets or restaurants. The AquAdvantage salmon was approved for marketing in Canada in 2016 and is available in supermarkets without special labeling. It is very popular with consumers.

A delay in the availability of cheaper salmon isn't the end of the world, but the FDA also unnecessarily and inexplicably delayed small-scale field trials of an innovative method to reduce the population of the mosquitoes that transmit Zika virus, yellow fever, dengue fever, and chikungunya. It uses a genetically engineered male *Aedes aegypti* mosquito constructed with a genetic defect that causes it to require a certain growth supplement for survival. When released, in the absence of the supplement the mosquitoes survive only long enough to mate with wild females and pass the lethal gene to their progeny, which soon die. Because male mosquitoes don't bite, they present no health risk and because more than 95% of the progeny die before they can reproduce, after a few generations, none persist in the environment. This approach has been successfully tested in several countries and has been commercialized in Brazil.

FDA took an unconscionable five years (2011–2016) to approve a single small-scale field test of this mosquito, and that came only after mounting pressure from the growing Zika virus threat and the consequent need to control *Ae. aegypti*. In August 2016, the agency finally approved a field trial at one site in the Florida Keys, some 160 miles from the Zika outbreak in Miami.

The use of the new animal drug regulatory pathway for the mosquito presented an insoluble legal conundrum for FDA, however. In order to approve it for marketing as a drug, regulators would have to conclude that genetic material that causes a male mosquito to self-destruct after producing defective, doomed offspring is *safe and effective for the mosquito*, as required by the Food, Drug, and Cosmetic Act. The FDA would have found itself in legal quicksand if its ultimate approval of the insect were challenged in court by environmentalists and anti-genetic-engineering activists, as would have been inevitable. After my coauthor and I first pointed out the "safe and effective" impossibility in the *Wall Street Journal* in 2016[22], the FDA in January 2017 ceded the regulation of

[21] Cohrssen, J.J. and Miller H.I. FDA is the wrong agency to regulate genetically engineered animals. Nature Biotechnology 35, 620–622 (2017). https://www.nature.com/articles/nbt.3915?WT.feed_name=subjects_biotechnology#ref4 [accessed 12 March 2019]

[22] Miller, H.I. and Cohrssen, J.J. The U.S. Is Botching the Zika Fight. Wall Street Journal. March 13, 2016. https://www.wsj.com/articles/the-u-s-is-botching-the-zika-fight-1457907116 [accessed 5 March 2019]

mosquitoes to the U.S. Environmental Protection Agency (EPA), an agency which does have the statutory authority to regulate insecticides.[23]

Early on, the FDA had confronted the question of how to regulate the new and increasing number of lines of genetically engineered laboratory animals created for medical research. The solution was simply to exempt them from the excruciating approval process by magisterially invoking "enforcement discretion," meaning the agency does not enforce requirements under the Food, Drug and Cosmetic Act. FDA also used enforcement discretion to obviate the need for review and approval of GloFish®, genetically engineered varieties of ornamental aquarium fish. Regulators' rationale was that the fish posed no threat to the food supply, and that there was no evidence that it posed any more threat to the environment or to public health than their unmodified counterparts.

Thus, as viewed through FDA's hyper-risk-averse lens, a small-scale field trial of a suicidal mosquito with essentially non-reproducing offspring, which would reduce the mosquito population for a clear public health benefit, poses a greater risk than the unregulated presence of unlimited numbers of reproducing aquarium fish and many lines of genetically engineered laboratory rodents.

The illogical and unnecessary expansiveness of FDA's use of the new animal drug regulatory pathway to regulate animals modified by recombinant DNA technology brings to mind a quip by former FDA Commissioner Frank Young, "Dogs bark, cows moo, and regulators regulate." And far from having seen the error of their ways, in January 2017 the FDA doubled down and announced their intention to further expand its regulatory turf to all "intentionally altered genomic DNA" in animals[24].

That expansion of a flawed policy has not yet been implemented, but prior to his departure earlier this year, former FDA Commissioner Scott Gottlieb announced his intention to do so.

Biopharming, (or "pharming").

For almost 30 years, academic and corporate scientists have used genetically engineered food and feed crops as miniature factories for producing pharmaceutical proteins and industrial chemicals that they do not make naturally. This technology, which goes by the punny name "biopharming," involves the insertion into plant cells of foreign genes coding for commercially important proteins, such as therapeutic proteins, monoclonal antibodies, and vaccines. To date, however, the FDA has not approved a single drug made by this method.

The concept is not new. Many common medicines, such as morphine, codeine, the laxative Metamucil, and the anti-cancer drug Taxol, are all purified from plants. But biopharming's great promise lies in using advanced genetic engineering techniques to make old plants do radically new things.

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[23] FDA. Draft Guidance for Industry Regulation of Intentionally Altered Genomic DNA in Animals, 2017. https://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM113903.pdf [accessed 5 March 2019]

[24] https://www.fda.gov/AnimalVeterinary/NewsEvents/CVMUpdates/ucm536949.htm [accessed 13 April 2019]

There is also great potential for cost-cutting in the process: The energy for product synthesis comes from the sun, and the primary raw materials are water and carbon dioxide. In addition, biopharming offers tremendous flexibility and economy when adjustments in production are necessary. Doubling the acreage of a crop requires far less capital than doubling the capacity of a bricks-and-mortar factory, making biopharmed drugs potentially much less expensive to produce than those made in conventional ways. As little as 2,000 acres can provide the substrate for a year's supply of some products. Grain from a biopharmed crop can be stored safely for long periods with no loss of activity. The quality of the final drug can meet the same standards as current pharmaceutical fermentation technology using microorganisms or cell culture.

Consider this description of the possible advantages of biopharming from the Federation of American Scientists:

> Production of biopharmaceuticals in transgenic plants may offer a cost-effective alternative to using engineered bacteria or mammalian cell culture. One advantage of biopharming is that plant cells possess the biochemical machinery needed to fold complex proteins and to perform the post-translational modifications (such as glycosylation, the addition of sugar molecules) required for full biological activity. Moreover, unlike mammalian cells, plants do not contain retroviruses and other infectious agents (such as prions) that cause disease in humans.[25]

But progress has been stalled by a combination of regulators' excessive risk aversion and the self-interested opposition of certain food manufacturers. The food industry fears that gene transfer or "volunteer" biopharmed plants in the field could cause vaccines, drugs, and other products to contaminate the food supply, triggering costly recalls and presenting thorny liability issues. Therefore, in a cynical demonstration of NIMBY-ism, food producers and their lobbyists have called for – and gotten -- Draconian regulation.

Most of USDA's restrictions on the cultivation of the biopharmed plants are excessively burdensome. For the most part, they impose highly prescriptive, one-size-fits-all "design" standards — as contrasted with "performance standards," which specify an end-point that must be achieved. They do not take into account the actual risks of a given situation.

A major impediment has been federal officials' zero-contamination mindset. They have tried to keep residues of biopharmed products out of the food chain, no matter how trivial the amount, or how negligible the risks. They have declined to establish non-zero tolerance levels for these substances, not because of any scientific or statutory restriction, but largely out of concern that opponents of biopharming would take advantage of such a move to proselytize against this new technology.

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[25] Federation of American Scientists. [undated] Biopharming: Turning Plants into Factories. https://fas.org/biosecurity/education/dualuse-agriculture/2.-agricultural-biotechnology/biopharming.html [accessed 5 March 2019]

The government's overly risk-averse approach can be justified on neither scientific nor political grounds. It appeases neither anti-biotech activists nor the food industry, both of which have simply used USDA's zero-tolerance policy as a rationale to demand even greater regulation and other strictures on biopharming.

Instead of punishing biopharming to the point of oblivion, we should reject the zero-tolerance mentality and approach safety scientifically and sensibly.

Even if biopharmed crops were to contaminate food crops, how likely is it that anyone would find harmful amounts of prescription drugs in his corn flakes, pasta, or tofu? A combination of factors — including natural selection, farmers pursuing their own commercial self-interest, liability concerns, and the vast size of the U.S. food supply — all militate against such a possibility.

Gene flow is a ubiquitous, biological fact of life. All crop plants have wild relatives somewhere, and some gene flow commonly occurs if the two populations are grown sufficiently close together. Thus, although genes could be transferred from a crop that has been modified to synthesize a pharmaceutical, the recipient plant is likely to proliferate only if genes that have moved confer a selective advantage. Such occurrences should be uncommon with biopharming because most often the added drug-producing gene will not confer on the recipient any selective advantage and could even place it at a selective *dis*advantage. Thus, if such a gene were to be transferred into a food crop, it might persist at a low level in the affected crop population for many generations, but we would expect its ability to proliferate and to cause significant contamination of the food crop to be limited.

Another relevant question is the persistence of post-biopharming volunteers. Michael Crawley and his co-workers compared the performance of four different recombinant DNA-modified versus conventional crops (rapeseed, potato, corn, and sugar beet) in natural habitats. They found that in no case were the recombinant plants (which were engineered for traits other than synthesis of pharmaceuticals) found to be more invasive or more persistent than their conventional counterparts. They also found "that arable crops are unlikely to survive for long outside cultivation." By the end of four years, of all the varieties cultivated in the study, only one variety of conventional potato persisted[26].

Gene transfer is an age-old consideration for farmers. Farmers in North America and elsewhere, who grow many hundreds of crops virtually all of which (save only wild mushrooms and wild berries) have been genetically improved in some way, have meticulously developed strategies for preventing pollen cross-contamination in the field — when and if it is necessary for commercial reasons. Traditionally, plant breeders' guidelines have called for keeping distinct varieties of corn, a wind-pollinated crop, at least 660 feet apart. At this distance, the two corn varieties will not hybridize to any great extent, even if small amounts of pollen might still drift between the fields. Even without government oversight, biopharmers themselves will strive to keep their specialty corn

[26] Crawley, M.J., S.L. Brown, R.S. Hails, D.D. Kohn, and M. Rees. "Biotechnology: Transgenic crops in natural habitats." Nature 409(2001):682-83.

sufficiently far from ordinary cornfields, lest their highly valuable drug-producing crops suffer contamination *from* the food crops.

Federal regulators could establish non-zero tolerance levels for biopharmed contaminants in the food supply. In some cases, such as for drugs that are neither orally active nor likely to be allergenic, contamination at any level should pose negligible risk (not unlike the level of concern about small amounts of pollen from a variety of yellow sweet corn pollinating white sweet corn in a nearby field).

For situations in which risk is uncertain or known to be non-negligible, one would base tolerances on animal toxicology studies, as regulators do for pesticide residues. Before approving a new pesticide, the EPA requires the manufacturer to examine how much of the chemical mice, rats, rabbits, and chickens can ingest or absorb without suffering any observable long-term effects following both acute and chronic exposure. Using highly conservative assumptions about both safety margins and the relevance of extrapolating high dosing of animals to very low exposures in humans, the EPA then builds in a safety margin of orders of magnitude to allow for differences between animals and humans and for possible enhanced susceptibility of children. With these kinds of assumptions, regulators create a huge safety margin — excessively huge, according to many experts — when they determine the maximum safe dose for humans. An analogous approach would substitute performance standards — that is, non-zero tolerances for carryover into food — for USDA's current design standards, could work for pharmaceutical contaminants, at least from a medical standpoint.

Although potentially workable, the outcome of this conservative approach to establishing tolerances — like the EPA's determination of acceptable pesticide residues, from which it is derived — will likely be overly risk-averse. Even in a worst-case scenario, by the time a food contaminated with a biopharmed substance passes a consumer's lips, it is unlikely to exert a significant effect. For personal injury to occur, several highly improbable events would have to happen.

First, the active drug substance would have to be present in the final food product — say, cornmeal or cornflakes— at sufficient levels to exert an adverse effect, the result of either direct toxicity or allergy. But there would have been a huge dilution effect as the tiny amounts of biopharmed corn stalks and leaves were pooled into the massive corn harvest. With very few exceptions (e.g., peanuts), even an allergic reaction requires more than a minuscule exposure. Second, the active agent would need to survive milling and other processing, and then cooking. Third, it would need to be orally active. The probability that *all* of these events would occur is extremely low.

Moreover, it is essential to consider the broader context of the kinds of chemicals that are commonly in our diet. We routinely consume hundreds of thousands of chemicals of all sorts — proteins, fats, carbohydrates, and minerals, among others. And pesticides: Professor Bruce N. Ames and his collaborators at the University of California Berkeley have estimated that each day, "on average, Americans ingest roughly 5,000 to 10,000 different natural pesticides and their breakdown

products," as well as about 2,000 milligrams of "burnt material, which is produced in usual cooking practices" and contains many carcinogens and mutagens (as measured in rodent tests).[27]

These observations emphasize the cardinal principle of toxicology — that the dose makes the poison. Unless we have the misfortune to eat something to which we are highly allergic, a poisonous mushroom, or a poorly dissected puffer fish, the chemicals present in food do not cause acute harm. The possible risks of adding one more chemical moiety to the diet, especially a minuscule amount, must be considered in that context. Except for extraordinary circumstances (for example, biopharming of an extremely potent toxin), there is no scientific justification for the kind of rigorous oversight that USDA imposes on biopharming.

On the occasion of USDA's announcement of the new restrictions on biopharmed crops in 2003, Agriculture Secretary Ann Veneman told reporters, "It's very important that we regulate in a way that allows this technology to proceed, so we can reap the benefits of it[28]." Instead, her department has since regulated in a way that will ensure that the field is stigmatized, that biopharming's research costs are hugely inflated, that only extremely high-value-added products will be candidates for development, and that consumers ultimately will see few biopharmed drugs in the pharmacy.

Nor is USDA the only regulatory obstacle. Early on, one company was able to surmount the technical and USDA hurdles only to be stymied by the FDA. Biotech company Ventria Bioscience created a variety of rice that synthesized two human proteins, lactoferrin and lysozyme. Once grown and harvested, the rice kernel is processed to extract and purify the proteins for use in an oral rehydration solution for treating diarrhea, which is surpassed only by respiratory diseases as the leading infectious killer of children under the age of five in developing countries.

The proteins have the same structure and functional properties as those found in natural breast milk, and the process for extracting them is analogous to that used routinely for the production of therapeutic proteins from organisms like bacteria and yeast.

Research in Peru showed that fortifying an oral rehydration solution with the proteins extracted from Ventria's rice substantially lessened the duration of diarrhea and reduced the rate of recurrence – a near-miraculous advance for people in the developing world.

But regulators can undo miracles, and they regularly do.

When Ventria approached the U.S. FDA in 2010 for recognition that these proteins are "generally recognized as safe," or GRAS (a regulatory term of art), it received no response. And without an endorsement by the FDA, the company was unwilling to market the product, and so it remains unavailable (except for laboratory research), tragically depriving children in developing countries of a life-saving therapy.

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[27] Ames, B., Profet, M., and Gold, L. Dietary pesticides (99.99% all natural), 1990. https://www.pnas.org/content/87/19/7777 [accessed 5 March 2019]

[28] Gillis, J. Rules on modified plants will be tougher. Washington Post. https://www.washingtonpost.com/archive/business/2003/03/07/rules-on-modified-plants-will-be-tougher/a89b290a-fb97-4a30-be38-4a476e473ce7/ [accessed 5 March 2019]

V. We Need Regulatory Reform

To state the obvious, none of this bodes well for robust corporate investment in this sector. And in these circumstances, there is little chance that pharmaceutical companies will develop products designed for less-developed countries where heat-stable, biopharmed drugs and vaccines could revolutionize health care.

Perhaps we should not be surprised to find how far regulators have strayed from a rational, science-based approach to plant-derived pharmaceuticals. The testing and commercialization of plants modified with molecular genetic engineering techniques are over-regulated generally, and it is much too easy for antagonists of biopharming to frighten consumers with images of hazardous drugs floating in children's breakfast cereals, while scientists invariably are careful to qualify their own statements and to refrain from blanket assurances that something is completely "safe."

Anti-biotech activists and the food industry constantly demand further tightening of the regulatory screws. These pressure groups want food plants to be off limits for biopharming, land once used to grow drug-producing crops to be dedicated solely to that purpose, and biopharmers to be indemnified against any damages they might cause under whatever scenarios their adversaries may dream up. Federal regulators, who are ostensibly committed to science-based regulation that discounts bias and the blandishments of special interests, already have erred on the side of risk-aversion and over-regulation.

If we are to reap what biopharming sows, we need a more reasonable, science-based policy.

Over four decades, modern biotechnology, also known as "genetic engineering (GE)" or "genetic modification (GM)," has produced monumental scientific, technological, economic, and humanitarian advances in medicine and agriculture. However, there is an old saying that if you want less of something, tax it, and over-regulation imposes what amounts to huge taxes on every manifestation of biotechnology. Those huge taxes have made R&D using genetic engineering less robust than it could have been; and some entire once-promising sectors have become non-viable, or at best, moribund. Had they not been stymied by wrong-headed, unscientific regulation that creates disincentives to R&D, all of the sectors described above (as well as others) could potentially have created the Next Big Things for food production, disease prevention, animal husbandry, pharmaceutical production, "biorational" pesticides, and bioremediation of toxic wastes. In addition, their innovations could potentially have improved existing technologies and products, making them more efficient, cost-effective, and sustainable.

If we are to unleash the ingenuity of scientists in academia and industry, we will need enlightened public policy that takes into consideration the centuries-long seamless continuum in the technologies for genetic improvement of all manner of organisms. This must include sweeping regulatory reform to make regulation scientifically defensible and risk-based – and how to achieve this is not a mystery.

The U.S. National Research Council concluded in 1987 that the product of genetic modification and selection should be the primary focus for making decisions about the risks of environmental

introduction of a plant or microorganism, not the process by which the products were obtained. Their report concluded that evaluation of experimental field testing should be based on three considerations: (1) Familiarity: that is, the sum total of knowledge about the traits of the organism and the test environment; (2) the ability to confine or control the spread of the organism, as necessary; and (3) the likelihood of harmful effects if the organism should escape control or confinement.

The essence of these principles is that the mere fact that an organism has been modified by recombinant DNA or other molecular techniques (including New Breeding Techniques, or NBTs) has no bearing on the degree of hazard or level of risk and therefore should not determine whether (or how stringently) the organism is regulated. Echoing and extending these and other scientific analyses, a 1992 report to the NIH from the U.S. National Biotechnology Policy Board concluded:

> The risks associated with biotechnology are not unique and tend to be associated with particular products and their applications, not with the production process or the technology per se. In fact, biotechnology processes tend to reduce risks because they are more precise and predictable. The health and environmental risks of not pursuing biotechnology-based solutions to the nation's problems are likely to be greater than the risks of going forward28 (emphasis added) .

Consider this syllogism:

> 1. There exists a long-standing consensus that molecular methods for genetic modification are essentially an extension, or refinement, of earlier, less precise techniques.
>
> 2. Effective regulation of products modified with pre-molecular techniques was in place prior to the advent of molecular techniques – e.g., in the United States, the Plant Pest Act; Toxic Substances Control Act; Federal Insecticide, Fungicide and Rodenticide Act; Noxious Weed Act; Food, Drug, and Cosmetics Act; and Public Health Service Act.
>
> 3. Therefore, there is no need for sui generis regulation of products that are more precisely crafted with molecular techniques.

Many groups of scientists and regulatory specialists have made credible proposals to rationalize regulation , such that triggers for oversight or for certain regulatory regimes would be based on the characteristics of products, rather than on the use of certain techniques, but as yet, there is nary a hint of adoption of that on the political horizon.

Meanwhile, the opportunity costs of flawed public policy continue to accrue. As University of California Berkeley agricultural economist David Zilberman and his colleagues observed, "The foregone benefits from these otherwise feasible production technologies are irreversible, both in the sense that past harvests have been lower than they would have been if the technology had been introduced and in the sense that yield growth is a cumulative process of which the onset has been delayed ."

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