AGRICULTURE

STUNTED HARVEST

Regulatory reform for biotechnology is a tough row to hoe.

BY JOHN J. COHRSSEN AND HENRY I. MILLER

President George H. W. Bush's loss in the 1992 general election was a setback to American agriculture. No longer did the nation have a White House eager to advance the use of relatively new techniques of molecular genetic engineering—the prototype of which was recombinant DNA technology, or "genetic modification" (GM). Instead, during Bill Clinton's administration, with agricultural biotechnology (and other federal technology policy) under the influence of Vice President Al Gore, the policy direction shifted toward the excessive and unnecessary regulation that he had sought unsuccessfully to impose while in Congress.

A prime example is the U.S. Food and Drug Administration's 1993 decision to expand its regulatory oversight to include all "genetically modified" animals, including insects. This move was surprising for a couple of reasons.

First, the FDA's Center for Veterinary Medicine decided to subject genetically engineered animals and insects to the same rigorous, burdensome pre-market research and approval procedures and regulations as new *veterinary drugs* such as antibiotics, pain relievers, and anti-flea medicines. The rationale was that the new DNA in the animal and any proteins it expresses are analogous to drugs that have been injected or ingested—even though animals with identical traits introduced by techniques such as natural breeding, artificial insemination, irradiation, or cloning would not be subject to any premarket review at all.

Second, the U.S. Department of Agriculture—not the FDA—had long been the agency most experienced in dealing with farm animals. And both the USDA and EPA had regulated insect biological control agents, which have been used successfully for more than half a century.

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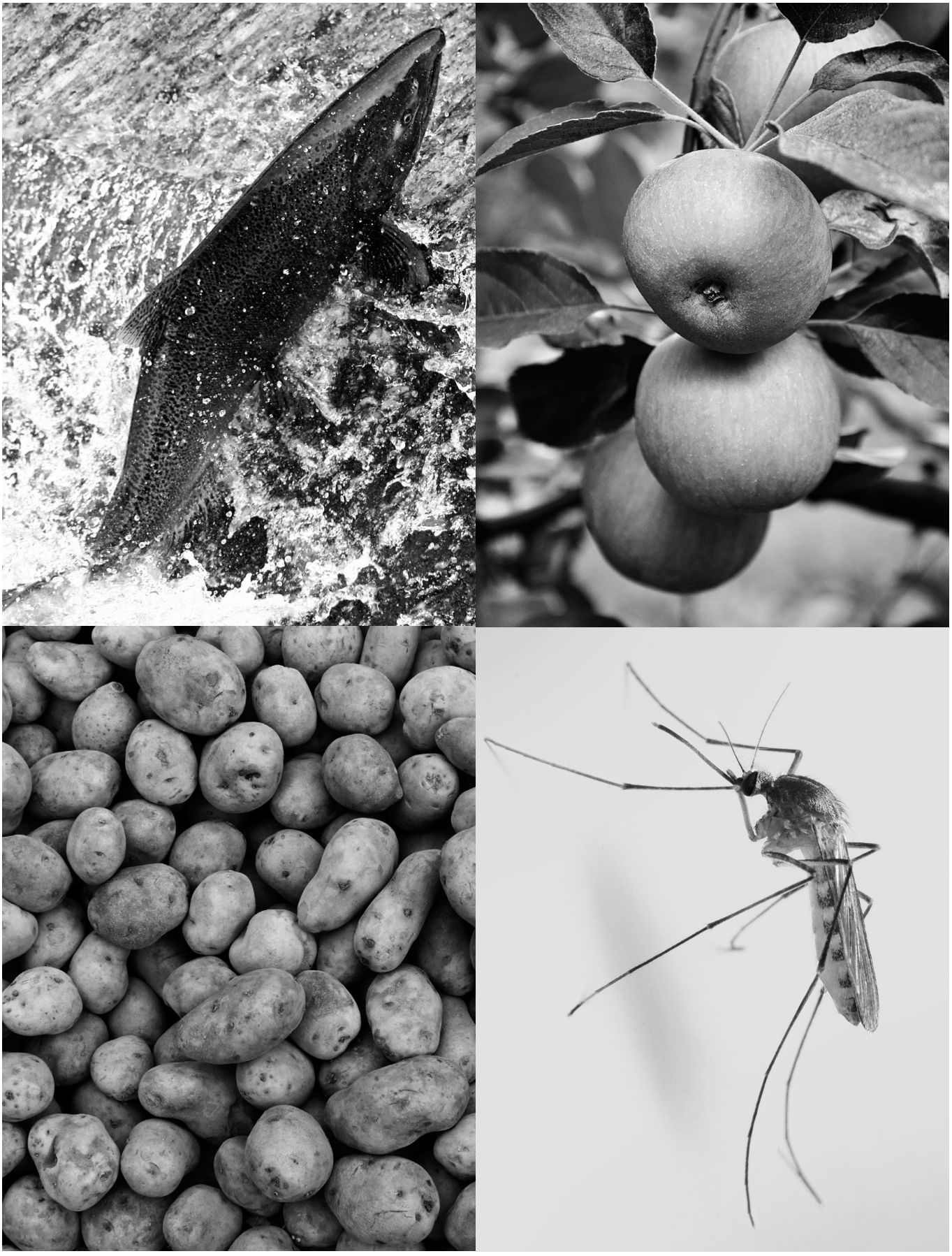
FISH STORY

The FDA's long review times have virtually obliterated the once-promising biotechnology sector of new, improved food animals. Under its authority to regulate veterinary drugs, the FDA dithered for more than 20 years in reviewing the AquAdvantage genetically engineered, faster-growing salmon. After the application had successfully fulfilled all FDA requirements, including an environmental assessment (the result of which was "no significant impact"), the decision was hijacked by the Obama White House, where it languished for three years before finally gaining approval this November.

The poor fish that treaded water in regulatory limbo for more than two decades is simply an Atlantic salmon with an added Chinook salmon growth hormone gene that is turned on all year long instead of only during the warmer months, as in nature. This roughly halves the salmon's time to maturity. The genetic change confers no detectable difference in the salmon's appearance, ultimate size, taste, or nutritional value; it just grows faster—a tremendous economic advantage in farming the fish in a closed water system. This will benefit consumers, who will have access to a greater supply and lower prices. The availability of the AquAdvantage salmon will also help to alleviate the pressure on populations of wild Atlantic and Pacific salmon, many species of which are threatened or endangered.

The FDA's exhaustive (and excessively lengthy) analysis concluded that the salmon has no detectable differences and that it "is as safe as food from conventional Atlantic salmon." Because the farmed fish will be sterile females and farmed inland in a closed system, they will be unable to affect the gene pool. (Even if they were to escape somehow, the fish would not adapt well in the wild because they are accustomed to being fed and coddled by humans.)



JPAVLISH (SALMON), REDSTALLION (APPLES), ABADONIAN (MOSQUITO), ERDEMERDEMLI (POTATOES)

This was neither a complicated nor difficult review. The genetic construction consisted of the addition of a gene from another salmon and a snippet of DNA from another fish, the ocean pout, that keeps the gene turned on continuously. There were no other detectable compositional differences. And the farming of only sterile females in a closed system will prevent the AquAdvantage salmon from replicating the horror of the science-gone-wrong B-movie spoof *Attack of the Killer Tomatoes*.

This excessively lengthy and uncertain regulation has forced some U.S. animal genetic engineering researchers to take their promising work to other countries such as Brazil and China, which offer a friendlier regulatory regime. That means once-highly-touted genetic modifications of animals—such as chickens and cows that produce less environmentally harmful manure, and pigs with muscles that have a higher ratio of protein to fat—are no longer on the horizon, at least in the United States.

PLANT PROBLEMS

Other foods have fared little better. As part of its voluntary review process for new genetically engineered plant varieties, the FDA has performed excruciatingly lengthy reviews instead of what should be routine, rapid evaluations. Recent examples include two and four years, respectively, to evaluate and approve bruise-resistant potatoes and non-browning apples, even though the genetic changes were minimal, well circumscribed, and did not involve the insertion of foreign or uncharacterized genetic material. Enzymatic browning is caused by the apple's intrinsic chemical reaction to cell injury, such as when the fruit is bitten or sliced, which ruptures the cells and triggers a chemical reaction between the enzyme polyphenol oxidase (PPO) and substances in the apple. A family of four genes controls the majority of PPO production. By down-regulating those genes, scientists were able to turn off more than 90 percent of PPO production, giving rise to the "Arctic Apple," which does not undergo enzymatic browning. The same enzyme-suppression technology has been used to produce the non-browning, low-acrylamide (a presumptive carcinogen) "Innate" potatoes, which are expected to arrive in fast-food outlets later this year.

Mercifully, those plants survived regulatory review, but the time spent on their reviews was absurd. Complex new pharmaceuticals that can be prescribed to millions of patients and have potentially significant side effects often are evaluated for safety and effectiveness and approved in less time. When one of the authors of this article, Henry Miller, was the FDA medical reviewer for Humulin (human insulin), the very first bioengineered drug, it was approved in five months. In contrast to the potato and apple reviews, the review of human insulin raised a number of potentially vexing health and environmental issues. The insulin is synthesized in bacteria—E. coli genetically engineered to synthesize the human protein—so there were concerns that the bacteria could colonize the human gut and the insulin they produced could cause hypoglycemia in drug company workers. There were also concerns about immunological side effects in patients from bacterial material in the purified, injected insulin. But those concerns were handled satisfactorily in less than half a year. In contrast to drugs, the vast majority of the FDA's reviews of genetically engineered foods are far less complex—so why do they take so long?

PROTECTION FROM DANGEROUS PESTS

Delaying the availability of faster-growing salmon or non-browning apples is hardly the end of the world, but the FDA is also dragging its feet on badly needed genetically engineered insect-control products that would prevent disease. A company called Oxitec has designed a live mosquito product to reduce the population of mosquitoes that carry dengue fever and chikungunya. It was approved in Brazil in 2014 after persuasive evidence of safety and efficacy in testing. But in the United States, the FDA has not yet granted permission even for field testing. After protracted delay, a limited, carefully controlled experimental study by the Florida Keys Mosquito Control District might finally start in the next few months.

Mosquito control is a major public health concern worldwide, with mosquito-borne diseases killing millions of people annually and causing suffering for many more. It takes only one bite from a disease-carrying mosquito to transmit a debilitating or deadly infection, and mosquitoes breed and multiply with astonishing speed. Given that there are no vaccines or drug treatments for illnesses like dengue fever, chikungunya, and West Nile virus, and that treatments for diseases like malaria are difficult to access in many at-risk areas, improved mechanisms for controlling mosquito populations are desperately needed to save lives.

Oxitec's approach involves the insertion of a lethal gene into insect embryos using molecular genetic engineering techniques. The modified mosquitoes can only be raised in a laboratory while kept alive by supplementing their diet with the antibiotic tetracycline. These modified mosquitoes, which are all male (and therefore don't bite people), are then released to mate with female mosquitoes in the wild. The males impart the lethal gene to their offspring, which, in the absence of the tetracycline supplement to keep them alive, die before adulthood. Continued releases of the

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engineered mosquitoes cause precipitous declines in wild mosquito populations and a corresponding drop in the diseases they cause.

The Oxitec insect-control technology has important applications for agriculture as well as public health. Last summer, the company announced successful early studies with a genetically modified diamondback moth that could control this destructive pest, which attacks cruciferous vegetables such as broccoli, cabbage, cauliflower, Brussels sprouts, and radishes.

Given the impaired evolutionary fitness of the Oxitec mosquitoes, the FDA's long delays in approving limited field trials are inexplicable. The reason that governments, industries, and academic sponsors perform field trials is to determine safety and efficacy, yet FDA regulators continue to stand in the way of obtaining these essential data.

In contrast to the interminable reviews by the FDA Center for Veterinary Medicine of the faster-maturing salmon and the Oxitec insect-control technology, those same FDA regulators have chosen to exercise "regulatory discretion" to forgo any review at all of the huge numbers of genetically engineered animals used extensively in biomedical research. They also exempted from regulation the widely available GloFish, a genetically engineered fluorescent zebra danio fish for aquariums.

REVISING THE FRAMEWORK

The Obama administration recently announced an ambitious White House initiative to update the 30-year-old Coordinated Framework for the Regulation of Biotechnology. (Disclosure: the coauthor of this article, John Cohrssen, was legal counsel to the White House working group that developed and implemented the 1986 Coordinated Framework.) The White House has directed the three regulatory agencies with biotechnology oversight—the EPA, FDA, and USDA—to update the Framework and develop a long-term strategy to ensure that the regulatory system is prepared for the future products of biotechnology, using a newly commissioned expert analysis of the biotechnology landscape.

By creating an environment that is friendly to biotechnology and the commercialization of products, the Obama White House has a unique opportunity to reduce the regulatory obstacles to continued U.S. advances in agriculture. Thirty years of experience with the molecular techniques and products of genetic engineering have proven their versatility, shown that new varieties of plants, animals, and microorganisms genetically engineered with molecular techniques have not posed any incremental risks compared to other techniques for genetic modification, and found that once-hypothesized risks have not materialized. Clearly, reforms are needed to make regulation scientifically defensible and risk-based, and to ensure that it provides acceptable cost-benefit.

The White House should adhere to the fundamental principles of the 1986 Coordinated Framework, which remain valid today for the oversight of research and development:

- New laws specifically for biotechnology are unnecessary and should be avoided. Biotechnology products can be regulated effectively under the mosaic of existing product-specific laws.
- Biotechnology regulation should avoid using a process-based scope, which by definition subjects all products within a defined process-based category to regulation, regardless of whether they are of high, moderate, low, or trivial risk. Such over-regulation not only retards innovation, but also feeds the self-perpetuating, incorrect perception that these products must pose a high risk because they are highly regulated.
- The degree (intrusiveness) of regulation should be commensurate with the risk of the product.

What sorts of regulatory changes are needed? The United States should return to the basic tenets of regulation prescribed more than two decades ago in the 1992 White House "scope" document, which supplemented the 1986 Coordinated Framework:

- The scope of regulation should be based on the risk-related characteristics of new products, not on the particular technology that enabled them.
- The scope of regulation should be based on evidence that the risk of a particular use of an organism for a particular application is unreasonable.
- A genetically engineered organism with new traits posing no greater risk than the unmodified organism should be subject to no greater scope of regulation.

As a practical matter, this means that to the extent appropriate, products of biotechnology should be regulated no more stringently than products developed by older and less precise manufacturing processes.

Twenty years of continuing White House and regulatory agencies' disregard of the Coordinated Framework and "scope" policies have led to the unnecessary, anti-competitive obstacles to U.S. agricultural applications of biotechnology that the Obama White House now supposedly seeks to address. In order to rationalize regulation, we need to return to a scope of regulation that is based on scientific evidence of an unreasonable risk—the overarching principle adopted by the White House to prevent unnecessary regulatory burdens in the first place. *R*