# Food, Drugs, and Consumer Products

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## GENETICALLY ENGINEERED FOODS

The safety of genetically engineered (GE) organisms has been studied extensively by dozens of the world's leading scientific bodies. Every one of them has concluded that the techniques give rise to no new or unique risks compared with conventional breeding methods, and that the ability to move individual genes between organisms actually makes the characteristics of genetically engineered products more precise and predictable, and therefore safer, than comparable products developed with more conventional breeding methods. Furthermore, the consensus among scientists who have studied genetic engineering—also known as biotechnology and gene-splicing techniques—holds that the evaluation of those products "does not require a fundamental change in established principles of food safety; nor does it require a different standard of safety" than those that apply to conventional foods. (See Institute of Food Technologists, *IFT Expert Report on Biotechnology and Foods*, Chicago: Institute of Food Technologists, 2000, p. 23.)

Nevertheless, genetically engineered plants and animals, and foods derived from them, have been subject to extensive regulatory requirements imposed by three different agencies in the United States: the U.S. Department of Agriculture (USDA), Environmental Protection Agency (EPA), and Food and Drug Administration (FDA). Essentially all new genetically engineered crop plants must undergo rigorous testing and be vetted by the agencies before they are put on the market, even as conventionally bred plants with identical characteristics are subject to no regulation at all.

Congress should reform the USDA approval process for genetically engineered plants to require that only those with known high-risk traits and those whose risks are unknown be approved before commercial use. The expensive and lengthy review process is scientifically unjustified and adds millions of dollars to the development costs of each new GE variety. The cost and complexity of complying with those regulatory strictures have concentrated GE product development in the hands of six major seed companies, and has made it uneconomical to use genetic engineering to develop improved varieties of all but major commodity crops, such as corn and soybeans. Small startup firms and university researchers simply cannot afford the regulatory costs associated with bringing a new GE crop to market.

Despite the overwhelmingly positive record of environmental and human safety, and the substantial burden of mandatory testing and regulatory review, some critics have demanded special labeling for GE foods. They argue that, even if GE foods are safe and nutritious, consumers want the additional information. Current FDA policy reserves mandatory labeling for food products whose characteristics have been changed in a way that affects safety and nutrition. Where a food product has been changed in a material way—such as an increase or decrease in vitamins, the addition of an allergen, or some other change that affects safety or nutritional value—the product label must note the specific change.

Labeling advocates have been unable to persuade the FDA, but they have had some success at the state level. Connecticut, Vermont, and Maine have enacted legislation that would require certain GE foods to be labeled as containing genetically engineered ingredients. Those laws, if fully implemented, would needlessly raise the cost of *all* foods, whether they contain GE ingredients or not. They are also unnecessary because a thriving market for voluntarily labeled non-GE foods has developed, providing those who wish to avoid genetically engineered ingredients plentiful choice in the marketplace. State labeling mandates are also unconstitutional, and they may be preempted by the Federal Food, Drug, and Cosmetic Act. Congress should clarify that act to clearly preempt state GE labeling mandates.

## Regulation of Genetically Engineered Plants and Foods

Dozens of scientific organizations, including the U.S. National Academies, American Association for the Advancement of Science, and Institute of Food Technologists, have carefully studied the safety of genetic engineering for consumers and the environment. All have concluded that the use of modern biotechnology, or gene-splicing techniques, gives rise to no new or unique risks compared with more conventional forms of breeding. In fact, say the experts, because the tools of genetic engineering are more precise and predictable, GE plants and foods derived from them will in many cases be safer than their conventionally bred counterparts.

**Congress should:**

- Reform the U.S. Department of Agriculture's approval processes for genetically engineered plants to require that only genetically engineered plants with high-risk traits be approved before commercial use.

In each of four studies conducted from 1989 to 2004, the National Research Council of the U.S. National Academies concluded that no scientific justification exists for regulating genetically engineered organisms any differently from conventionally bred varieties. The safety of a new plant variety has solely to do with the characteristics of the plant that is being modified, the specific traits that are added, and the local environment into which it is being introduced, regardless of whether genetic engineering or a more conventional breeding method is used to modify the plant. Nevertheless, to ameliorate public concerns about gene splicing, the U.S. Department of Agriculture and the Environmental Protection Agency each developed regulatory frameworks during the 1980s that require premarket approval for nearly all new genetically engineered plant varieties, regardless of the safety of the traits incorporated into individual plants.

Under the Plant Protection Act, the USDA treats essentially all GE plants as potential plant pests—organisms that may be injurious to agriculture—until they have been extensively tested under stringent rules, found not to be pests, and then "deregulated" by the department (7 CFR 340). Two decades of practical, commercial experience with GE crops have shown early concerns to be unwarranted, and approved varieties have an admirable record of consumer and environmental safety. Furthermore, the USDA has not once had to reject an application because the new variety was in any way unsafe. Yet instead of being comforted by that admirable safety record, the USDA's response has been to demand more testing and to lengthen the time it takes to review deregulation applications.

From 1992 to 1999, the USDA took an average of fewer than six months to deregulate 50 new GE varieties—after several years of required testing were completed for each. Regulatory review times grew steadily beginning in the 2000s, and the department now takes an average of over two full years to deregulate a new variety, despite a much smaller number of applications being submitted. (See USDA Animal and Plant Health Inspection Service, "Petitions for Determination of Nonregulated Status," http://www.aphis.usda.gov/biotechnology/petitions_table_pending.shtml.) Regulatory hurdles alone add between $6 mil-

lion and $15 million to development costs for each new variety, a burden that only large seed companies can afford—and then only for high-value commodity crops. Regulatory compliance costs for GE crops can often exceed the entire market value of most fruit and vegetable species. And small startup firms and university-based researchers simply cannot afford to bring any new GE varieties to market.

The current regulatory system for genetically engineered crop varieties cannot be justified scientifically. It singles out the more precise techniques of gene splicing for added scrutiny, even as crops bred using less precise, and arguably less safe, methods—such as induced DNA mutation and forced hybridization of different plant species—go entirely unregulated. Crops bred to withstand herbicides or with added resistance to certain pests are heavily regulated if they are produced with gene-splicing techniques, but the very same traits are not regulated at all if the crop was, for example, exposed to radiation in order to mutate the plant's DNA.

What is needed is a regulatory apparatus that focuses on new plant traits, not breeding method, and increases the amount of testing and scrutiny as the riskiness of individual traits rises. Congress should instruct the USDA to exempt low-risk traits, such as herbicide tolerance, from Plant Protection Act regulation and to focus solely on traits known to pose potential hazards to humans or the environment, as well as traits that are genuinely novel, whose risks are unknown.

Expert: Gregory Conko

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## GE Food Labeling

The U.S. Food and Drug Administration's policy on labeling foods derived from new plant varieties, introduced in 1992, follows the advice of major scientific bodies and is premised on the view that what determines the safety, wholesomeness, and nutritional value of a food is its characteristics, not the breeding method used to develop it. (See Food and Drug Administration, "Statement of Policy: Foods Derived from New Plant Varieties," *Federal Register* 57, May 29, 1992, 22,984–23,005.)

**Congress should:**

- Codify the Food and Drug Administration's current labeling policy for food products, under which special labeling is necessary only when a food's characteristics have been altered in a material way, and preempt state GE food labeling requirements.

All breeding methods—from simple hybridization to the most modern biotechnology-based techniques—have the potential to introduce significant changes in the composition of foods. But well-known and easily performed testing methods are sufficient to determine a food's nutritional value and safety. Therefore, according to FDA policy, food producers have a legal obligation to ensure that new food plant varieties are safe for human and animal consumption, but special labeling specific to GE foods is not required.

Producers have a legal obligation to note on labels any time a food has been changed in a way that might be material to consumer safety and nutrition. Such changes might include a higher or lower level of vitamins or other nutrients, fats, carbohydrates, and other components beyond the normal variability present in conventional counterparts. Material changes could also include the introduction of an allergen or other potentially deleterious substance, or even a change in a food's taste, smell, texture, or its storage, handling, or preparation requirements.

If a new food product has been changed in any of those ways, its label must alert consumers to the modification, regardless of whether that change was made using genetic engineering or another breeding method. Importantly, it is not sufficient merely to state what *breeding method* was used to develop the product; the label must state what *change* has been made.

Ever since the first genetically engineered food products were put on the market—cheeses produced with an engineered clotting agent called chymosin in 1990 and milk from cows given an engineered version of the natural bovine growth hormone somatotropin in 1993—some critics have demanded that those products be labeled to indicate that gene splicing was used in their production. (See Center for Veterinary Medicine, U.S. Food and Drug Administration, "BST Update," *CVM Update*, March 21, 1996.) However, the FDA has resisted calls for special labeling of those genetically engineered foods that have been tested extensively for safety and have been found not to differ in any material way from their conventional counterparts. And where a food was changed in a material way, such as the introduction of a protein that could be allergenic or a modification that would produce healthier fats in cooking oils, the alteration would have to be included on the product's label.

The agency, which relies on mandatory labeling to alert consumers about important safety and nutritional changes, concluded that a mandatory GE label would falsely lead consumers to believe there is an important safety concern regarding genetic engineering when, in fact, there is none. According to the American Association for the Advancement of Science, "Legally mandating such a label can only serve to mislead and falsely alarm consumers." (See American Association for the Advancement of Science, "Statement by the AAAS Board of Directors on Labeling of Genetically Modified Foods," October 20, 2012, http://www.aaas.org/sites/default/files/AAAS_GM_statement.pdf.)

Labeling advocates respond that a large majority of consumers say they support mandatory GE labeling, and that, regardless of whether GE foods are safe, consumers have a right to choose. However, the demand for information has spawned a thriving market for voluntary labeling that indicates the absence of GE ingredients. Thousands of foods labeled "non-GE" can be found in grocery stores around the country, and both advocacy organizations and consumer groups have introduced pocket shopping guides and smartphone apps to help shoppers exercise the choice many say they want.

Finding no success with FDA, mandatory labeling advocates have turned to lobbying state governments instead. Bills and ballot initiatives to require labeling have been introduced in at least 25 states. Most have been rejected, but Connecticut, Vermont, and Maine have enacted such legislation. Those laws are unnecessary, given the availability of voluntary labeling information. If fully implemented, they will raise costs and prices for both GE and non-GE foods.

Furthermore, they are legally dubious on various grounds. They are unconstitutional because, as federal courts have concluded, satisfying consumer curiosity is not a governmental interest sufficient to overcome the producers' First Amendment rights not to include extraneous information on labels. (See *International Dairy Foods Association v. Amestoy*, 92 F.3d 67 (2nd Cir. 1996).) And state GE labeling laws may also be preempted by the Federal Food, Drug, and Cosmetic Act, as one federal court has concluded (*Briseno v. ConAgra Foods Inc.*, No. 2:11-cv-05379 (C.D. Cal., November 23, 2011)).

Because the provisions of the Federal Food, Drug, and Cosmetic Act that preempt state labeling laws are ambiguous, supporters of FDA's current policy introduced a bill in 2014 explicitly to preempt state GE labeling rules: the Safe and Accurate Food Labeling Act (H.R. 4432). To build support for the legislation, the bill would also increase the stringency of the FDA's existing safety review for new genetically engineered food products. Yet the overwhelming majority of food safety scientists agree that no scientific justification exists for regulating genetically engineered organisms any differently from conventionally bred varieties, so even FDA's existing regulatory framework is unnecessary. Congress should clarify that the Federal Food, Drug, and Cosmetic Act does preempt state GE labeling laws, but it should resist needless calls to increase the already-burdensome regulation of genetically engineered foods.

Expert: Gregory Conko

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## CONSUMER FOOD CHOICE

### Federal Food, Drug, and Cosmetic Act

The U.S. Food and Drug Administration is trying to control Americans' diets by abusing its power to regulate food additives. In November 2013, the FDA published a tentative proposal to remove the "generally recognized as safe" (GRAS) status of partially hydrogenated vegetable oils, also known as PHOs or trans fats. Removal would mean that food producers would need to prove that PHOs are "safe" before being allowed to use the ingredients in their products—a hurdle that is likely impossible, given that FDA has indicated that it believes there is no safe level of trans fat consumption. Thus, the revocation of GRAS status is a way of creating a de facto ban on the ingredient. And public health activists and consumer advocacy organizations are pressuring the FDA to use its GRAS authority to ban or restrict additional ingredients, including sugars, salt, caffeine, and many others.

**Congress should:**

- Stop the Food and Drug Administration's march toward invasive control by amending the Federal Food, Drug, and Cosmetic Act to clarify that the agency has authority to limit or ban only those ingredients that are either acutely harmful to human health or have health risks that are cumulative over time, cannot be identified by the consumer, and cannot be mitigated through dietary or lifestyle choices.

Although there is some evidence that high levels of trans fat consumption may increase the risk of cardiovascular disease, a ban is regulatory overkill. In 2002, Americans consumed an average of 4.6 grams of PHOs a day. Yet in 2012, average daily consumption dropped to approximately 1 gram a day (or 0.5 percent of total daily calories) (FDA, "FDA Takes Step to Further Reduce *Trans* Fats in Processed Foods," news release, November 7, 2013, http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm373939.htm). Despite the dramatic voluntary decline in consumption and the fact that research has examined mainly the effects of high levels of consumption—and those that looked at consumption below 2 percent of daily calorie intake found no adverse effects—the FDA contends that any level of trans fat consumption increases the risk of cardiovascular disease and death and therefore warrants total elimination from Americans' diet. (See Dennis Strayer et al., *Food Fats and Oils*, 9th ed., Washington, DC: Institute of Shortening and Edible Oils, 2005, 20.)

Under the Federal Food, Drug, and Cosmetic Act, the FDA has the authority to approve additives for use in food if it determines they are safe. Revoking the GRAS status of PHOs because long-term overuse may lead to an increased risk of developing certain health conditions would be a significant shift in policy. By attempting to stop individuals from consuming ingredients that could be unhealthful if overused, the agency is trying to protect consumers not from dangerous foods, but from what it sees as bad choices.

The FDA appears to be basing its policies not on sound scientific evidence but on the wishes of extremist public health activists. For example, in 2012, Robert Lustig, a pediatric endocrinologist at the University of California, San Francisco, declared that sugar was a toxin and that the agency should consider removing its GRAS status, thus treating it like an additive that companies would need to prove is safe before they can add it to their products. In essence, the FDA sees trans fats as the low-hanging fruit in its broader effort to establish its authority to limit or ban ingredients that are not harmful, but that may be *unhealthful* if overconsumed. If successful, public health advocates will push the FDA to do the same with their true targets: sugar, salt, and caffeine in manufactured foods. What constitutes our diet ought to be the choice of every individual.

Experts: Michelle Minton, Gregory Conko

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### "Nudging" Policies

In July 2014, Rep. Rosa DeLauro (D-Conn.) introduced the Sugar-Sweetened Beverages Tax Act, which would impose a na-

tional tax on sugary beverages and use the revenue to partially fund the Affordable Care Act. The goal of the tax is to make soda expensive enough that consumers will choose other beverages, leading to a reduction in obesity. Yet soda taxes do not result in more than trivial weight reductions because those who consume the largest amounts of sugar-sweetened beverages appear to respond least to higher prices, or they substitute other high-calorie foods and beverages for the taxed sugar-sweetened products. Sin taxes simply raise prices for low- and middle-income families at the grocery store.

**Congress should:**

- Reject proposals to impose soda taxes or any other attempt to use "sin taxes" to engineer individuals' choices.
- Monitor the proceedings of the Dietary Guidelines Advisory Committee (DGAC) to ensure that the next edition of its *Nutritional Guidelines for Americans* is based on nutritional science, that the committee participants are not politically motivated, and that no federal agency uses the *Guidelines* as a tool to socially engineer choices that ought to be left to individuals.

Although economic theory would suggest that higher prices generated by soda taxes should lead to lower consumption, real-world evidence suggests that sin taxes have only a minuscule effect on consumption of sugar-sweetened beverages. In part, the reason is that any decrease in soda consumption is offset by increased consumption of other sweet or calorie-dense drinks, such as fruit juices and whole milk. Most of the research predicting sizable benefits from soda taxes assumes that individuals will reduce soda consumption and not change any other consumption patterns.

Economic studies estimate that every 10 percent increase in soda prices may result in an 8 percent to 10 percent reduction in soda consumption, but that higher-calorie substitutes are consumed instead. Research on the effect of even very high taxes on sugary beverages found that 20 percent and 40 percent taxes on all sugar-sweetened beverages resulted in an average annual weight loss of only 0.7 to 1.3 pounds per person, respectively. Those studies also show that the weight reductions were driven almost entirely by middle-income households, and that sin taxes failed to alter the weight of lower-income houses at all.

In addition to taxes, another tool currently being used by public health nannies is the Dietary Guidelines Advisory Committee, which meets every five years and publishes the *Dietary Guidelines for Americans*. That publication is meant to outline what dietary and lifestyle choices promote good health. Based on the testimony at this year's meetings, the 2015 *Guidelines* will be more politically motivated and less science-based than ever before. DGAC members include many at the forefront of nanny-state activism, such as Sonia Angell, who led the effort to ban trans fats in New York City restaurants and has proposed using taxation and regulation to push Americans toward a plant-based diet.

Among other dubious suggestions, the DGAC's 2015 recommendations on sodium intake will likely echo the 2010 *Guidelines*, which advised adults to reduce their sodium intake to fewer than 2,300 milligrams a day (fewer than 1,500 milligrams for adults over 51), perpetuating the misguided "war on salt." However, a comprehensive report by the Institute of Medicine, commissioned by the U.S. Centers for Disease Control and Prevention (CDC), concluded that there was no evidence of a benefit to reducing sodium intake to below 2,300 milligrams, and that some groups might *increase* their risk of death by consuming fewer than 1,840 milligrams a day (Institute of Medicine, *Sodium Intake in Populations: Assessment of Evidence*, Washington, DC: National Academies Press, 2013). And a landmark 2011 study published in the *Journal of the American Medical Association* found that, although higher sodium consumption was associated with slightly higher blood pressure, lower sodium consumption was associated with higher cardiovascular disease mortality. The third of study subjects who consumed the least salt had three times the mortality as the third who consumed the most salt.

Although the *Guidelines* primarily affect school lunches, the military, and food stamp programs, it informs the policy of the FDA, USDA, National Institutes of Health, and CDC. For instance, when proposing to revoke the GRAS status of trans fats, the FDA relied heavily on the conclusions of the 2010 *Dietary Guidelines for Americans.*

Experts: Michelle Minton, Gregory Conko

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## DRUGS AND DEVICE APPROVAL

Patients benefit from the thousands of available pharmaceuticals and medical devices on the market today. But the Food and Drug Administration's (FDA) overly cautious testing and approval process, and demands that such treatments meet a near-perfect level of safety, are often counterproductive. Patients can be injured if the FDA approves a treatment that is later found to be unsafe. But they are also harmed when needed treatments are delayed by regulatory hurdles, or when the cost and complexity of securing approval mean that promising new treatments are never presented for agency evaluation.

Safety concerns that arise after a drug or device is approved result in startling headlines and congressional hearings. That consequence incentivizes FDA regulators to be overly cautious in their decision making, demanding more trials with more patients, raising costs, and prolonging development times. Meanwhile, sick patients who are denied treatment options that may save their lives receive far too little attention. In 2012, Congress required the FDA to more formally measure the life-saving and health-enhancing benefits of new drugs and to explain how it weighed those benefits when making approval decisions. That process should be strengthened and implemented more quickly.

Congress should also require the FDA to update its decades-old rules for testing new drugs. Randomized, placebo-controlled clinical trials are good for detecting when medical interventions have large effects on populations of similar patients. But the homogeneous patient pools and tightly controlled clinical environments associated with randomized trials do not reflect real-world practice and outcomes very well. Existing clinical trial rules do not sufficiently account for variability among patients and differences in patient outcomes that are discovered only after clinical trials are begun. The rules prevent fast-paced adaptive learning in favor of more and longer trials with more patients, even though the latter are ill suited to discovering a drug's safety and benefit profile.

Individual patients disagree about how much risk they are willing to tolerate in order to obtain a new treatment's potential benefits. Therefore, the FDA's one-size-fits-all approval process means that decisions will be too cautious for some and not cautious enough for others. Those who view the agency's approval process as too quick may freely choose to use only products that have been on the market for several years with a well-established record of safety and efficacy. Those who seek access to medical products before the FDA has fully approved them have little or no choice. In theory, the agency's Expanded Access, or "compassionate use," program provides an option for terminally ill patients who cannot be enrolled in a clinical trial to access treatments that have not yet been approved. In practice, however, the process for seeking a compassionate use exemption is complicated, time-consuming, and burdensome, which means that many patients are denied a genuine opportunity to choose.

### Benefit-Risk Assessment

The U.S. Food and Drug Administration's statutory mission is to ensure that "substantial evidence" is generated from "adequate and well-controlled investigations" for a new drug's safety and efficacy (21 U.S.C. 355[d], Federal Food Drug, and Cosmetic Act, § 505). But no drug is perfectly safe, in the sense that it has no negative side effects. And each drug affects individual patients differently. So the best we can expect from FDA decision making is a determination that an approved product's benefits outweigh its risks for the typical patient.

**Congress should:**

- Accelerate the FDA's implementation of the structured benefit-risk assessment process for new drugs mandated by the FDA Safety and Improvement Act of 2012, and require the agency to more fully consider the views of affected patients in approval decisions.

Even after extensive clinical testing, the net effects of a new medicine are not always well characterized. Drugs are generally tested in only a few thousand patients, leaving much unknown at the time an approval or disapproval decision must be made. In practice, the FDA has long been highly cautious when confronted with such uncertainty, even as patients with life-threatening or severely debilitating diseases have expressed a willingness to tolerate greater risk in exchange for the potential benefits of new therapies. Moreover, the agency's process

for assessing and balancing the benefits and risks of medicines is largely ad hoc, informal, and qualitative, relying primarily on the intuitive judgment of its medical review staff and expert advisory committees. As a consequence, agency officials tend to make incompletely informed judgment calls that substitute their own risk aversion for the judgments of affected patients. And because the FDA is not required to explain how it weighs risks and benefits, neither the public nor Congress has sufficient information on which to evaluate the agency's performance.

A 2007 Institute of Medicine report concluded that a more standardized and robust analysis of risks and benefits could improve FDA decision making with attendant improvements for public health. So, as a part of the FDA Safety and Improvement Act of 2012, Congress instructed the agency to "implement a structured risk-benefit assessment framework in the new-drug approval process to facilitate the balanced consideration of benefits and risks, a consistent and systematic approach to the discussion and regulatory decision making, and the communication of the benefits and risks of new drugs" (Food and Drug Administration Safety and Innovation Act, Public Law 112-144, Section 905). It also instructed the agency to consider in its new-drug approval decisions the views that affected patients themselves place on the value of various benefits and risks associated with new treatment options. However, the statutory text provided no other guidance to the agency, leaving substantial discretion regarding the assessment's structure and implementation.

In 2013, the FDA initiated a five-year plan to develop and implement the risk-benefit assessments, and it has begun to gather information and input from patient organizations to incorporate those views in approval decisions. (See FDA, "Structured Approach to Benefit-Risk Assessment in Drug Regulatory Decision-Making: Draft PDUFA V Implementation Plan," February 2013, http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM329758.pdf.) Implementation has proceeded very slowly, however, and it remains unclear how the agency will assess the demand by patients for more rapid introduction of innovative treatment options, and what value it will place on those demands. Both the development process and its application to individual approval decisions should be expedited and made more transparent.

Benefit-risk analysis can help decision makers better understand the likely consequences of their actions, and it can lead to greater transparency and accountability by forcing FDA officials to make their assumptions about the value of specific benefits and drawbacks of specific risks explicit. Ultimately, the purpose of formalized and published benefit-risk assessments is to put FDA's expert judgments on record, explain the agency's reasons for approving or denying approval for new products, and hold those decisions up to public scrutiny.

Expert: Gregory Conko

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## Clinical Trials

A 2007 report by the U.S. Food and Drug Administration's Science Board concluded that "FDA's evaluation methods have remained largely unchanged over the last half-century," and that "[i]nadequately trained scientists are generally risk-averse, and tend to give no decision, a slow decision or even worse, the wrong decision on regulatory approval or disapproval" (FDA Science Board, "FDA Science and Mission at

Risk: Report of the Subcommittee on Science and Technology," 2007, 3, 5).

**Congress should:**

- Modernize and streamline the FDA's clinical testing protocols and approval process to take greater advantage of adaptive trial design and active learning.

First developed more than 50 years ago, the FDA's approach to clinical testing—which relies on multiple trials in three phases of testing—is premised on the belief that patients will have similar responses to medical interventions, and that a drug's benefits and side effects will be easy to identify given a large enough test population of patients with similar health and physical characteristics. We now know, however, that similar patients often respond quite differently to the same medications, and that the homogeneous patient pools and tightly controlled clinical environments associated with randomized trials do not reflect real-world practice and outcomes very well.

The FDA's main response to that phenomenon has been to demand more data from more patients to provide greater confidence in its decision making. That approach has caused the length of clinical trials to grow and the median number of tests conducted per patient (such as routine exams, blood tests, and X-rays) to rise. Those new hurdles have also made it more difficult to enroll patients in trials and to keep them in the trials until completion.

Randomized controlled trials are ill suited for detecting and testing subtle differences that occur in small patient subpopulations, which make them poor tools for fast-paced, adaptive learning. To minimize the occurrence of hindsight bias in data analysis, clinical trials begin with a hypothesis and a carefully constructed methodology for testing that hypothesis. When an unexpected or idiosyncratic effect is detected among a subpopulation of the test group, the FDA typically demands that the manufacturer form a new hypothesis and initiate an entirely new, often superfluous trial. In the process, adaptive learning is short-circuited, and the cost of drug development rises still further.

Today, new computational tools, better understanding of disease pathways, the development of biomarkers to predict drug effects, and other technological advances are enabling the use of innovative methods that could improve clinical trial quality. Those tools, combined with adaptive clinical trial designs—which allow researchers to learn as trials are in progress and, in turn, change dosing regimens or isolate patient subpopulations that respond especially well or poorly to the test drug—could help trial sponsors collect better, more robust data from fewer patients and in a shorter time. The FDA has announced its willingness to consider those new methods, but in a way that requires greater testing and more cautious analysis (FDA, "Adaptive Design Clinical Trials for Drugs and Biologics: Draft Guidance," February 2010, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM201790.pdf). If the rules for adaptive trials remain too rigid, they could prevent patients from reaping the full benefits of the innovative methodologies.

The FDA must be more willing to allow flexibility in trial designs and to approve new drugs with fewer trials and fewer patients. Augmenting that accelerated testing process with more robust postapproval monitoring could lead to greater overall patient safety. After all, new drugs are generally tested on only a few thousand patients. The full benefit-risk profile of medicines is often unknown until they have been approved and prescribed to tens of thousands, or millions, of patients in real-world settings. So additional testing before approval simply cannot be expected to reveal a drug's true risks or benefits. Indeed, the rate of drug withdrawals remained essentially unchanged between 1971 and 2004, despite rising and falling trial requirements and approval times during that period. (See Center for Drug Evaluation and Research, "2003 Report to the Nation: Improving Public Health through Human Drugs," Food and Drug Administration, U.S. Department of Health and Human Services, April 23, 2004.)

Since 1992, the FDA has had an "accelerated approval" track for drugs that treat serious conditions for which no other treatments are available. In certain circumstances, such drugs may be granted limited approvals after a single Phase III trial (or on rare occasions, after Phase II trials are complete), under the condition that the manufacturer continue conducting additional trials to demonstrate safety and efficacy. The agency may also designate drugs intended

to treat serious conditions with an unmet medical need as "breakthrough therapies," which may be approved on the basis of a substantial reduction in symptoms or other serious consequences of the disease, rather than evidence that the product cures the disease per se. Those programs have greatly accelerated the introduction of promising new drugs on the market, but the FDA should be more aggressive in combining technologically sophisticated adaptive trial designs with the accelerated approval and breakthrough therapy pathways.

Using aggressive oversight—and, if necessary, additional legislation—Congress should encourage the FDA to permit greater flexibility in clinical trial methodology. It should also encourage the agency to approve drugs sooner and to demand fewer unnecessary trials—substituting more robust post-approval monitoring for the lengthier testing that is unlikely to reveal more about a drug's safety profile.

Expert: Gregory Conko

### *For Further Reading*

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## Patient Choice

When making safety evaluations, the U.S. Food and Drug Administration is required, by statute, to determine the appropriate balance between patient safety and medical product effectiveness. The agency cannot know the optimal risk-benefit balance for every patient because each patient will have different views about how much risk and how many side effects he or she is willing to bear in order to use a new treatment that could alleviate symptoms or cure a disease. Therefore, it is important for individual patients to have more opportunities to choose a medical treatment that meets their unique health status and risk tolerance. Currently, few patients ever have the option of choosing a drug or medical device that has not satisfied FDA's risk-benefit preferences.

**Congress should:**

- Reduce burdens on patients wishing to use FDA's Expanded Access, or "compassionate use," programs and create other opportunities for patients to choose not-yet-approved drugs.

Some patients with unmet medical needs may be eligible to enroll in a clinical trial to test a new medicine or medical device. But because of the need for homogeneous patient populations in clinical trials, many simply do not qualify for enrollment because of their age, comorbidities, prior treatments, and the progression of their disease.

Under current law, the FDA may grant Expanded Access, or so-called compassionate use exemptions, for patients with serious or life-threatening diseases ("Expanded Access to Investigational Drugs for Treatment Use," 21 CFR § 312 Subpart I [2013]). But the process for seeking Expanded Access is complicated and time-consuming. It requires the patient's physician to submit a detailed application, which the FDA estimates will take 100 hours to complete. (See FDA, "IND Applications for Clinical Treatment [Expanded Access]: Overview," October 4, 2013, http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm351748.htm; and FDA, "Investigational New Drug Application Form," http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083533.pdf.)

The manufacturer must also consent to provide the drug, and the paperwork burden for manufacturers is also considerable. In addition, many manufacturers are concerned that granting such access could jeopardize their ability to enroll the clinical

trials needed for FDA approval. And many manufacturers are often reluctant to agree to Expanded Access use, because they may charge patients only the direct costs "incurred by a sponsor that can be specifically and exclusively attributed to providing the drug." (See Food and Drug Administration, "Charging for Investigational Drugs under an Investigational New Drug Application, Final Rule," 74 *Federal Register* 40872, August 13, 2009, http://www.gpo.gov/fdsys/pkg/FR-2009-08-13/pdf/E9-19004.pdf.) The paperwork and resource burden on manufacturers of making experimental drugs available are considerable, and those restrictions often make manufacturers unwilling to participate in compassionate use programs.

Although the FDA does eventually grant nearly all Expanded Access requests that are submitted by patients and manufacturers, that approval often comes many months after applications are submitted, jeopardizing the patient's best opportunity to treat the disease at a stage early enough to be effective. And in the end, the hurdles involved with seeking such an Expanded Access exemption mean that few patients ever even try to use that route. Despite substantial demand for early access to unapproved drugs, only about 1,000 patients each year navigate the process and complete an Expanded Access request.

Individual patients and their doctors are in a far better position than FDA bureaucrats to judge whether the uncertain risk and benefit of new treatments are warranted. The agency should focus on providing them with the information that is, and is not, known about experimental treatments and should permit patients to weigh the potential risks on their own, rather than on restricting patient choice.

Congress has previously examined proposals to reform the Expanded Access process by streamlining the paperwork burden and removing FDA's discretion to deny compassionate use to patients who meet basic qualifications. One such example is the Compassionate Access Act (H.R. 4732), introduced in 2010 by Rep. Diane Watson (D-Calif.). That bill, and others like it, have never reached a floor vote, but they provide Congress with a template to use as the starting point to develop legislation to make it easier for patients to seek and be granted Expanded Access exemptions. In addition, Congress should consider other options for giving patients access to not-yet-approved drugs and devices.

Expert: Gregory Conko

## CONSUMER PRODUCTS

Many useful consumer products may soon disappear from the market, and innovation may dwindle, as policy makers—federal, state, and local—expand precautionary policies to ban and eliminate useful chemicals. For example, regulators and state lawmakers are placing some products on "chemicals of concern" lists, simply because they have the potential to cause adverse health effects at relatively high levels, even though risks are negligible or nonexistent at the very low levels at which those chemicals appear in consumer products.

Listing requires little consideration of the science, but it invites unnecessary regulation and, by scaring consumers about insignificant risks, even encourages voluntary elimination of many products. Such random elimination of technologies wastes the human ingenuity and investment that went into making those goods and denies society their benefits. Innovators must then divert resources to find substitute products, which may themselves pose new risks. The result is a poorer, potentially more dangerous world.

**Congress should:**

- Avoid legislation that creates or encourages arbitrary "chemicals of concern" lists or imposes scientifically unfounded precautionary bans on valuable chemicals.
- Promote legislation requiring federal agencies to employ risk- and-science-based standards for all chemical regulations.
- Increase oversight activity of the U.S. Environmental Protection Agency's (EPA) development of concern lists, as well as voluntary programs that characterize chemical risk without regulatory due process.

Congress and various regulatory bodies are advancing regulations purely on the basis of tenuous hazard profiles rather than on genuine risk. "Hazard" simply represents the potential for danger given specific circumstances or exposures. For example, water can be hazardous because excessive consumption can produce fatal water intoxification or hyponatremia, yet there is no need to regulate it or place it on a concern list. But that same approach is being used to demonize many synthetic chemicals that have been used safely in consumer products for decades.

EPA officials, for example, are developing a "chemicals of concern" list on the basis of hazard profiles for a number of chemicals to increase market pressure for their elimination without having to navigate the regulatory process to impose bans or other regulations. The agency also uses its Design for the Environment program to push companies to phase out certain chemicals because of their hazard profiles alone. The EPA can get away without proper reviews and standards because that program is considered voluntary.

Members of Congress have also introduced several bills to ban chemicals without regard to the potential adverse impacts of such bans. For example, during the 113th Congress, Sen. Chuck Schumer (D-N.Y.) introduced the Children and Firefighters Protection Act of 2014 (S. 2811), which would ban the use of 10 flame-retardant chemicals at levels of about 1,000 parts per million in children's products or upholstered furniture—and which would empower the Consumer Product Safety Commission to ban more. It does not require any evaluation of the benefits of those products, nor does it consider whether their absence will increase fire risks.

But we do know that fire risks are real and substantial. For example, the National Fire Protection Association reports that, in 2013, there were 1.24 million fires in the United States that caused 3,240 deaths, 15,925 injuries, and $11.5 billion in property damage. Meanwhile, there is little evidence that anyone has died or suffered significant injuries from trace chemicals found in furniture or clothing. It is dangerous to advance policies that ban such chemicals without demanding that regulators first consider the potential that, without those products, fires may burn more quickly, may be hotter, and may produce more deaths.

Also during the 113th Congress, Sen. Ed Markey (D-Mass.) introduced the Ban Poisonous Additives Act of 2014 (S. 2572), which would eliminate the chemical bisphenol A (BPA) from food containers. The resins that line food containers made with

BPA prevent the development of deadly pathogens in our food supply, protecting consumers from potentially deadly bacteria like E. coli. Because BPA resins have no good alternatives, BPA bans could increase food spoilage and serious food-borne illnesses. Meanwhile, the overwhelming body of evidence supports comprehensive scientific evaluations that have all found that the many benefits of that chemical outweigh its very low risks.

Self-styled consumer activist groups are also pushing the Food and Drug Administration to ban the antibacterial chemical triclosan, which has been used safely for more than four decades in soap, toothpaste, and antibacterial gels. Despite good scientific evidence that the chemical reduces bacteria-related risks, many manufacturers are voluntarily removing it from consumer products, and several states are even considering bans.

Valuable consumer products are lost to such rash bans, the cost of which is passed on to consumers. Congress needs to increase its oversight of the EPA, FDA, and other regulatory agencies that mischaracterize the risk profiles of various products by placing them on concern lists or use hazard-based classification systems.

Lawmakers should oppose legislation that bans products on political and unscientific grounds. In addition, lawmakers should pass regulatory reforms that set rulemaking standards for agencies that regulate chemicals in consumer products. Those standards should require that, before issuing a regulation, such agencies demonstrate that (a) significant risks exist at actual human exposure levels on the basis of the weight of the evidence and the best available, peer-reviewed science; (b) the risks of potential substitute products are unlikely to be higher than those of the existing product; (c) economic costs do not outweigh the benefits; and (d) the regulation chosen is the least burdensome one that meets their public health goal.

Experts: Angela Logomasini

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