Comments of Consumers Union on the
Food and Drug Administration Notice: Clarifying Current Roles and Responsibilities Described in the Coordinated Framework for the Regulation of Biotechnology and Developing a Long-Term Strategy for the Regulation of the Products of Biotechnology
Docket No. FDA-2015-N-3403

Prepared by Michael Hansen, Ph.D.
Senior Scientist

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Consumers Union[1] (CU), the policy and advocacy arm of Consumer Reports, welcomes the opportunity to comment on the Food and Drug Administration (FDA) notice on *Clarifying Current Roles and Responsibilities Described in the Coordinated Framework for the Regulation of Biotechnology and Developing a Long-Term Strategy for the Regulation of the Products of Biotechnology*. We believe that the current Coordinated Framework is seriously flawed because it does not take into account the potential novel risks associated with genetically engineered organisms and utilizes existing laws are adequate to deal with the products of biotechnology.

Our bottom line is that all genetically engineered (GE) organisms (whether a plant, animal, insect or microorganism) should be required to go through systematic assessments of human and environmental effects and indirect economic effects (such as contamination of organic or non-GE crops leading to rejection in foreign markets, spread of resistant pests, etc.) before such products are allowed on the market. To increase transparency, these assessments should be made available to the public for comment. All products from GE organisms that are sold to the consumer should be required to be labeled as such, both to ensure consumer choice as well as to track potential unintended health effects. Companies that develop GE organisms should be required to disclose any GE trait, marker genes, or other genetic constructs that might be present in a commercial, GE seed product, including traits and genes from obsolete, no longer marketed traits. In addition, the definition of genetic engineering should be broad enough to include all the newer genetic engineering techniques such as RNAi or the new gene-editing technologies (e.g., CRISPR-cas9, TALEN, ZNF, meganucleases, etc.). More detailed comments are below.

The Consolidated Framework is Broken

Under the Consolidated Framework, agencies were charged with using existing statutory authorities to regulate GE organisms, under the assumption that the existing laws were adequate and could fully cover the risks and impacts of GE organisms. But some of the risks of GE organisms are novel and not covered by existing laws, which has led the agencies to force the GE

[1] Consumers Union is the policy and advocacy arm of Consumer Reports. Consumers Union is an expert, independent, nonprofit organization whose mission is to work for a fair, just, and safe marketplace for all consumers and to empower consumers to protect themselves. It conducts this work in the areas of telecommunications reform, health reform, food and product safety, financial reform, and other areas. Consumer Reports is the world's largest independent product-testing organization. Using its more than 50 labs, auto test center, and survey research center, the nonprofit organization rates thousands of products and services annually. Founded in 1936, Consumer Reports has over 8 million subscribers to its magazine, website, and other publications.

organisms to fit their regulatory authority. In a sense, the Consolidated Framework ended up with various agencies trying to fit "square pegs into round holes." In addition, the agencies have not used the statutory authority they do have to adequately regulate GE organisms.

The U.S. Department of Agriculture (USDA) regulates GE plants under the Plant Protection Act (PPA) and thus only really considers whether GE plants might act as weeds. In addition, the USDA's definition of a GE plant is that it must have a plant pest component (e.g., genetic material from a plant pest) to be considered a "regulated article." Thus, if a plant is genetically engineered, but does not contain genetic material from a plant pest, the plant is not considered a regulated article (e.g., 7 CFR 340.2). The first wave of GE crops allowed on the market—the herbicide tolerant crops and *Bacillus thuringiensis* (Bt) crops—invariably contained plant pest DNA, since the vast majority used the cauliflower mosaic virus 35s promoter and/or contained DNA from *Agrobacterium tumefaciens* and so underwent some scrutiny by USDA. However, use of newer genetic engineering technologies, such as the gene-editing techniques, has meant that GE plants can be produced that do not contain plant pest DNA. The developers of these new GE plants can simply write to USDA and receive a letter from USDA saying these new GE plants are not "regulated articles." To date, USDA has sent letters exempting over 30 GE plants—including glyphosate-tolerant Kentucky bluegrass, glyphosate-tolerant Augustine grass, glyphosate-tolerant tall fescue grass, and Loblolly pine trees with increased wood density—from *any* USDA oversight.[2] Since the new gene-editing technologies do not require the use of plant pest DNA, we suspect that the majority of new GE plants will escape any oversight by USDA during the field trial process. These GE plants that escape regulatory scrutiny by USDA, may still be considered to be GE plants by either EPA or FDA, meaning that the agencies may have differing definitions of what constitutes a GE plant.

Furthermore, while the USDA is limited by the PPA in what it can define as a GE plant (e.g., a regulated article), it does not use the statutory authority it does have to sufficiently look at risks. Thus, the noxious weed provisions of the PPA could be used to look at a range of potential environmental and trade risks, such as those caused by contamination of non-GE or organic crops.

USDA regulates GE insects under the Animal Plant Health Protection Act (APHA), which was designed to protect livestock and poultry, including farmed fish from animal diseases. Thus, for GE insects, USDA only considers whether the GE insect has an impact on communicable diseases of livestock and poultry, rather than taking into account the broader environmental or ecological impacts of releasing a GE insect.

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[2] At https://www.aphis.usda.gov/wps/portal/aphis/ourfocus/biotechnology/am-i-regulated/!ut/p/a1/pZPLUsIwFIafxUWXJadpIcEdiFAKqCPe2k0nLaGNtk1Ng4hPb2Dc4AV0zC7J95_85xIUoQcUVexFZEwLWbFiu486cXDpY6cPeDwanfdhfDGcXpFJgAG3DRDuAfPuuQHuhjM6Je4kIPt6SnyA8fAymPQHcxcGzoceflg9OKa_RxGK0krXOkchq3PRxKmsNK90XIhEMbWxoGGxXKl4KdNVY0EipOZpXslCZuaSlbawFc9WBdN8sY1Wp2KBQidtU-wwz-52PM_2HL6wE2BgAxACXdwhKaafs_9q74_V2wcm7d_pz0Y93yNTUy-PYhgP-v6AdGfGSeeYfle9I_3bAYcadPCRbQ474IDJ0GRBfoxggPkf2xL8om5Yzc5mmQnLdG6LainRw6dRMJB4fH6OembAtiP1qg3y_wkz5rJCJrvPFfaqxKXGheJLrrhqrZQ5zrWum1MLLFiv161MyqzgrVSWFnwnyWVjjO2TqC5vb0vqboSwn679t5tleU813bhFdnLyDsniLzo!/?1dmy&urile=wcm%3apath%3a%2Faphis_content_library%2Fsa_our_focus%2Fbiotechnology%2Fam-i-regulated%2Fregulated%2Barticle%2Bletters%2Bof%2Binquiry%2Fregulated%2Barticle%2Bletters%2Bof%2Binquiry.

The Environmental Protection Agency (EPA) regulates GE microorganisms under the Toxic Substances Control Act, while the risk of GE microorganisms that can reproduce and spread is fundamentally different that the risk of toxic chemicals, which cannot reproduce.

FDA regulates GE animals as new animal drugs, which does not make sense, but at least there is a mandatory safety assessment, although FDA does not have the expertise to look at the environmental impacts of these GE animals. For GE plants, FDA is regulating them under the 1992 Statement of Policy which says that genetic engineering is just an extension of conventional breeding, does not raise new health risks, and that safety assessments are not required. There is only a voluntary safety consultation process where there is cursory agency review and FDA does not make any conclusions about the safety of the GE plant. In essence, FDA has allowed companies to argue that the new GE crops are generally recognized as safe (GRAS).

In 2001 FDA issues a proposed Premarket Notice for Bioengineered Foods, which directly contradicted the 1992 Statement of Policy since it admitted that genetic engineering does differ from conventional breeding and does raise potential health issues such that FDA proposed requiring data on each separate transformation event: "[B]ecause some rDNA-induced unintended changes are specific to a transformational event [e.g., those resulting from insertional mutagenesis], FDA believes that it needs to be provided with information about foods from all separate transformational events, even when the agency has been provided with information about foods from rDNA-modified plants with the same intended trait and has had no questions about such foods. *In contrast, the agency does not believe that it needs to receive information about foods from plants derived through narrow crosses* [e.g. conventional breeding]," italics added.[3] In other words, FDA admitted that there is a difference between genetic engineering and traditional breeding. However the 2001 Notice was never finalized and FDA is still following the 1992 policy. . Though neither the 1992 nor the 2001 policy have been finalized, we urge FDA to take the approach of the 2001 Premarket Notice which regulates GE plants by the process used to create them and requires separate safety assessments for each transformation event.

Although FDA has allowed companies to argue that the GE materials and their expression products are GRAS, FDA could have regulated GE foods under the food additive provisions of the Federal Food, Drug, and Cosmetic Act (FFDCA), which would have mandated more extensive testing and a safety approval by the agency.

The bottom line is that the Coordinated Framework should be updated to ensure that all GE organisms are adequately assessed for human, environmental, and indirect economic impacts.

Scope of Technologies Falling Under the Framework/Regulate by Process, Not Product

[3] Pg. 4711 in FDA. Premarket Notice Concerning Bioengineered Foods. Federal Register January 18, 2001. Federal Register Vol. 66(12): pp. 4706 – 4738. At: http://www.gpo.gov/fdsys/pkg/FR-2001-01-18/pdf/01-1046.pdf.

The Coordinated Framework does not recognize the new risks associated with genetic engineering and so the trigger for regulatory oversight is based on the attributes of the GE organism, not the process (e.g., genetic engineering) used to create them. This has led to problems such as USDA allowing many GE plants (those produced without plant pest DNA) to go completely unregulated, or FDA's decision to allow GE plants to be treated as GRAS. It also means that some of the risks associated with GE organisms (e.g., genetic contamination, resistant pests) go unaddressed.

We believe that regulations should be based on the process used to create the GE organism and not the attributes of the GE organism. Thus, the trigger for regulatory oversight should include all current and future genetic engineering technologies that either move foreign or novel DNA into the genome of a plant, animal, or microorganism, or target or alter the expression of genes naturally in a plant, animal, or microbial genome. As a start, the U.S. could use as its definition of "modern biotechnology," as laid out by Codex Alimentarius in the *Principles for the Risk Analysis of Foods Derived from Modern Biotechnology* (CAC/GL 44, 2003): "'Modern biotechnology' means the application of: *i) In vitro* nucleic acid techniques, including recombinant deoxyribonucleic acid (DNA) and direct injection of nucleic acid into cells or organelles, or ii) Fusion of cells beyond the taxonomic family, that overcome natural physiological reproductive or recombinant barriers and that are not techniques used in traditional breeding and selection."

GE Crop Risk Assessments

In conducting risk assessments to assure the safety of GE crop technology, we recommend that federal agencies:

- Take into account both the novel proteins and other compounds produced by or associated with a GE plant, as well as any other related chemicals that must or will typically be used in conjunction with the GE crop technology. These will, of course, include all herbicides associated with an herbicide-tolerant crop variety, as well as seed treatments recognized as essential for a farmer to bring a GE crop to harvest.

- Assess the risks of novel allergens and toxins, as well as pleiotropic or epigenetic impacts or other unintended effects.

- Assure that the protein or trait, or plant that is tested is, in fact, identical to the one in the GE plant being evaluated. Thus, EPA should not allow a Bt toxin produced in *E. coli* to be used in toxicity tests in place of the Bt toxin as extracted from the Bt plant.

- Rigorously adhere to the results of GE crop and isoline side-by-side trials, in judging whether the composition and/or nutrient levels in GE cultivars have changed. Agencies should not accept nor consider the range of "natural variation" in nutrient levels in the crop species under different conditions when conducting statistical tests of changes in nutrient levels in properly designed, side-by-side trials.

- Conduct animal feeding studies, in which the diet of the control animals consists of the near-isolines of the GE crop being tested, and which has been grown in the same environment. Agencies should not use animals fed with other non-GE varieties of the crop tested as a comparator. In addition, the diet of the control animals should be tested for the presence of contamination from GE crops and the herbicides used with the herbicide-tolerant crops, which could have a confounding effect on the results.

- Develop new, detailed test requirements for stacked varieties, acknowledging that multiple traits can lead to adverse interactions just as treatment with multiple medications can lead to drug interactions and contraindications.

- For any new trait that expresses a novel protein in the edible portions of GE plants, require long-term (at least 2-year or two-generation) lab animal feeding experiments designed to detect chronic diseases like cancer and metabolic diseases, as well as subtle changes in physiology, developmental, and reproductive performance and outcomes.

- Require and support work by government or independent scientists tracking the metabolic breakdown pathways of all novel proteins in the edible portions of GE plants, including at least tier 1 toxicity and allergenicity testing of primary metabolites and breakdown products.

Calibrate Risk Assessments and Risk Mitigation Provisions to the Scale of Adoption

We also recommend that agencies recognize that the scale of adoption of any GE crop technology will drive the nature and magnitude of any possible adverse environmental or public health consequences. Agencies should seek from technology developers a prospective degree of market penetration within five years of approval, including estimates of the regions where newly approved GE seeds will be planted. They should also limit approvals to these estimates, and base risk assessments and regulatory actions on the scope of possible, approved adoption over such five-year periods. If technology developers envision market demand exceeding initial approval levels, a petition must be submitted estimating the future trajectory of adoption, including specification of regions where adoption will exceed initial projections, so that agencies can reconsider the data needed to evaluate potential environmental and human health risks. Approval for expanding adoption should not be granted until risk assessments are updated based on data compiled from initial plantings, estimates of any incremental environmental or food chain increases in the levels of internal or directly associated compounds linked to the GE technology, and updated assessments of direct and/or indirect human health, environmental, or agronomic impacts.

Dealing with the Risks Arising from the Emergence and Spread of Resistant Organisms

Furthermore, we recommend that all federal agencies:

- Be directed to impose mandatory requirements phasing out the use of antibiotic-related marker genes in newly developed GE plants and trees by 2017.

- Require resistance risk assessments as part of any application for approval of a new or existing, pest management-related GE technology.

- Subject the submitted resistance risk assessment to an independent review organized by the EPA's pesticide Scientific Advisory Committee (SAP). Agencies should also specify as part of any deregulation decisions the mandatory steps that all adopters of the technology must adhere to in order to prevent the emergence and spread of resistant organisms.

We also recommend that the EPA and USDA develop, in consultation with a resistance risk advisory committee formed under the EPA SAP, a post-approval resistance-monitoring program to be carried out by independent scientists and laboratories and paid for by fees imposed on the technology developer.

Initial approvals should be contingent on scientific assessment of proposed resistance risk management plans and agency judgments regarding the expected impact of such plans on the risk of resistance emerging.

Resistance thresholds in target pests and/or secondary organisms should be included in the initial decision documents. Such thresholds should set forth when additional, second-tier resistance management provisions will become mandatory. Second-tier resistance management practices should be set forth in the initial approval document, and agreed upon prior to approval by the technology developer.

If such additional resistance risk management provisions prove ineffective in reversing the frequency of resistant organisms, the USDA and/or EPA should impose reductions in maximum allowed acres that can be planted in the next crop season, coupled with tier three resistance management practices. If the EPA SAP resistant management advisory committee cannot agree on a recommended, tier three set of resistance management practices sufficient to reverse the spread of resistance, steps to limit adoption on any given field to once every two or three years should be invoked.

In the event such limitations on the frequency of use prove ineffective in reversing the geographic scope of land area impacted by resistant organisms, the duration between allowed uses on any given field should be expanded to the point deemed by the EPA SAP resistance management advisory committee as sufficient to stop the spread of resistance.

Covering Indirect Costs Triggered by GE Crop technology

We also recommend that all future deregulation decisions should include a quantitative estimate of the economic consequences of any potential adverse impact associated with the newly proposed GE technology. Such adverse economic impacts might arise from herbicide drift or carryover; the spread of resistant pests; gene flow to farms producing crops for GE-sensitive markets; disruption of exports to GE-sensitive markets in the U.S. or abroad, and; the

costs associated with avoiding contamination with GE genes and/or testing for, isolating, and disposing of contaminated seeds or crops.

The federal agency responsible for approval of conditions of use of any new GE technology should include a fee upon the technology developer based on each unit of sale (e.g. a pound or bag of seed). The fee per unit of seed sold should be set at a level deemed by the government as sufficient to cover possible, near-term (i.e., next three years) adverse economic effects of the technology. The agency should review the fee structure on an annual basis, taking into account the funds available to cover future claims, the frequency and size of claims already paid for by the fund, and the possible future frequency and scope of claims, given the degree of adoption of the technology.

Facilitate Independent Research and Refinement of Risk Assessments

Furthermore, we recommend that federal agencies should require, as part of the application process, a guarantee from technology developers that requests for isolines and/or genetic markers and probes, or other technical information necessary to conduct risks assessments on GE technologies, will be provided either to responsible federal agencies, and/or to independent researchers without imposition of any restrictions on what research can be conducted, or when and how results may be reported.

The FDA should publicly disclose the data provided by GE organism developers and allow for public comments on these data before the GE organisms are allowed on the market.

In addition, before any field trial of a GE plant, USDA should require the exact sequence information of the inserted genetic material so that USDA can detect possible contamination during the field trial stage. Presently, USDA does not require such sequence information, so there is no way to detect contamination. In addition, the locations of GE field trials should be disclosed so that neighboring farmers can guard against genetic contamination.

All applications for approval of GE technologies expressing novel proteins or constituents in engineered plants, animals, or microorganisms should include in the initial application a publicly accessible, verified method for the detection of the modified proteins or constituents in the crop, animal, or microbe, as well as in the bodily fluids and tissues of concern in the animals, including humans, likely to ingest the novel proteins or constituents.

Require Labeling of GE Products Sold to Consumers

We believe that <u>all</u> genetically engineered food should be labeled, for several reasons. First, at least two different labeling provisions of the FFDCA--the ingredients labeling provision (Sec. 403(i)) and the "material fact" provision prohibiting "false or misleading" labeling (Sec. 403(a))--would seem to require it.

Presently, FDA maintains that a "material fact" means that there must be some change in nutritional value, organoleptic properties, or functional characteristics. We strongly disagree with this view. . In the past, FDA has required labeling under the "material fact" analysis that did not

entail a change in nutritional value, organoleptic properties, or functional characteristics. A material fact, in FDA's view, is information that consumers view as important. If such information is not on the label, then the label is considered to be misleading. FDA articulated this position in a final rule that required labeling of irradiated foods,[4] even though the FDA had ruled that irradiated foods were safe. FDA has stated in this final rule on food irradiation that the large number of respondents who asked for labeling of retail products was one factor indicative of the materiality of food irradiation: "*Whether information is material under section 201(n) of the act depends not on the abstract worth of the information but on whether consumers view such information as important and whether the omission of label information may mislead a consumer. The large number of consumer comments requesting retail labeling attest to the significance placed on such labeling by consumers*"[5] emphasis added. **Thus, materiality clearly does not always include "some change in nutritional value, organoleptic properties, or functional characteristics."**

FDA has used the material fact rationale to require source labeling for protein hydrolysates. Labeling the source of protein hydrolysates was required because of the concern of vegetarians and observant Jews and Muslims. As the FDA stated, "the food source of a protein hydrolysate is information of material importance for a person who desires to avoid certain foods for religious or cultural reasons."[6]

Further, in 2007, FDA proposed a revision to their labeling requirements for irradiated foods, such that labeling would only be required on those irradiated foods in which the irradiation has led to a "material change"—defined as a "change in the organoleptic, nutritional or functional properties"—in the food that is not obvious to the consumer at the point of purchase.[7] Thus, not all irradiated food would be required to be labeled. This proposed revision to the irradiation labeling standard went nowhere. However, this attempted weakening of the food irradiation labeling standard suggests that FDA is now trying to narrow the concept of "materiality," possibly to avoid the labeling of GE foods.

In addition, FDA should require labeling to insure that any unexpected or unintended effects of GE come to FDA attention. Such labeling is authorized by international guidelines developed by the Codex Alimentarius Commission. In recent years, certain drugs approved by FDA as safe have turned out to have unexpected health effects after they were widely used by consumers. It is essential to label GE plants and animals so that any unexpected effects will be recognized and consumer health protected.

Assure Full Disclosure of GE Traits in Seed Products

We also recommend that agencies require companies to fully disclose any GE traits, marker genes, or other genetic constructs that might be present in a commercial, GE seed product, including traits and genes from obsolete, no longer marketed traits.

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[4] 51 Fed. Reg. 13376-88, (April 18, 1986).
[5] Pg. 13380 in IBID
[6] 56 Fed. Reg. 28592 (June 21, 1991).
[7] 72 Fed. Reg. 16291-16306 (April 4, 2007). At: http://www.fda.gov/ohrms/dockets/98fr/07-1636.htm

Conclusion

In conclusion, we believe that the Consolidated Framework is seriously flawed because it fails to recognize the potential novel risks associated with genetically engineered organisms and treats existing laws as adequate to deal with the products of biotechnology. We are especially concerned that newer genetic engineering technologies that may pose health and environmental risks, such as RNAi and gene editing techniques, are escaping even limited regulatory review under the Consolidated Framework because this already stretched and contorted legal patchwork cannot be stretched any further to cover them. The Consolidated Framework is simply incapable of coping with modern scientific advances in biotechnology.

We believe that all genetically engineered (GE) organisms (whether a plant, animal, insect or microorganism) should be required to go through systematic assessments of human and environmental effects and indirect economic effects (such as contamination of organic or non-GE crops leading to rejection in foreign markets, spread of resistant pests, etc.) before such products are allowed on the market. To increase transparency, these assessments should be made available to the public for comment. All products from such GE organisms that are sold to the consumer should be required to be labeled, both to ensure consumer choice as well as to track potential unintended health effects. A new legal framework is needed to accomplish these goals.