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National Science and Technology Council
Emerging Technologies Interagency Policy Coordination Committee
Office of Science and Technology Policy
1650 Pennsylvania Avenue NW.
Washington, DC 20504

Re: Docket No. FDA-2015-N-3403

I am writing with reference to Docket No. FDA-2015-N-3403 "for 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; Request for Information." I am a Distinguished Professor of Plant Sciences and Director of the Seed Biotechnology Center at the University of California at Davis. I am a specialist in seed biology, genetics and biotechnology have been engaged in scientific research and teaching in these topics for the past 34 years. I would like to submit the following comments for consideration in updating the regulatory procedures associated with the applications of biotechnology, particularly in agriculture. While the request for information is focused primarily on how the federal agencies should coordinate their regulatory activities, those questions in my opinion are secondary to the fundamental rationale under which all of those agencies operate. I will therefore comment on the overall approach toward regulation of the products of biotechnology as embodied in the Coordinated Framework (CF) in 1986 and revised in 1992 and also provide specific recommendations that would enable the Biotechnology Regulatory Services to achieve the overall goal of providing "regulatory approaches that protect health and the environment while reducing regulatory burdens and avoiding unjustifiably inhibiting innovation, stigmatizing new technologies, or creating trade barriers" as set forth in the Memorandum on Modernizing the Regulatory System for Biotechnology Products (Holdren et al., 2015).

To begin my comments, I include by reference here a paper published in *Nature Biotechnology* in 2005 specifically on the topic under consideration (Bradford et al., 2005). It is disturbing that nothing has changed in the regulatory system in the decade since that paper was published, or in fact since even earlier analyses were published (Barton et al., 1997), and thus everything in these papers remains fully relevant today. This includes the key proposals discussed and supported fully by scientific evidence, including: 1) deregulating the transgenic process *per se*; 2) rationalizing the scientific basis for transgenic regulation; 3) exempting selected transgenes and classes of transgenic modification from regulation; 4) creating regulatory classes in proportion to potential risk; and 5) eliminating the event-specific basis of transgenic regulation. I also note the following statement in the Memorandum referenced above: "While the current regulatory system for the products of biotechnology effectively protects health and the

environment, in some cases unnecessary costs and burdens associated with uncertainty about agency jurisdiction, lack of predictability of timeframes for review, and other processes have arisen. These costs and burdens have limited the ability of small and mid-sized companies to navigate the regulatory process and of the public to understand easily how the safety of these products is assured; and, accordingly, they have the potential to reduce economic growth, innovation, and competitiveness." These negative consequences have been documented in detail almost a decade ago, particularly with respect to specialty crops that suffer the most daunting regulatory burdens under the current system (Alston et al., 2006; Bradford et al., 2006; Kalaitzandonakes et al., 2007; Dobres, 2008), and again, the situation remains unchanged, with the regulatory system for products produced using biotechnology still reducing economic growth, innovation and competitiveness.

I also include by reference here prior comments that I submitted on November 21, 2008 under Docket No. APHIS-2008-0023 in response to a previous proposal for revision of the regulatory procedures governing evaluation and release of the products of biotechnology. Those comments referred to specific proposals for revision of the regulatory system for products of biotechnology, and would still be relevant should those proposals be considered in the current review.

As stated in the OSTP Memorandum, the intent of the current review is to "update the CF [Coordinated Framework] to clarify the current roles and responsibilities of the agencies that regulate the products of biotechnology," which had previously affirmed "that Federal oversight should focus on the characteristics of the product and the environment into which it is being introduced, rather than the process by which the product is created." This principle underlying the CF remains valid, rational and in accordance with scientific consensus. However, this principle has never been implemented in practice, as all plants and animals in which certain techniques of gene transfer and modification have been utilized are automatically required to undergo a regulatory permit and/or review process, regardless of the characteristics of the product. The use of recombinant DNA (rDNA) or genetic engineering (GE) techniques is the sole criterion by which a plant product is determined to be subject to pre-market review by the USDA-APHIS Biotechnology Regulatory Service (BRS) with respect to whether it is a potential weed or plant pest. A plant developed using non-GE methods of breeding is not required to seek such pre-market determination, regardless of the characteristics of the product, while GE plants are required to do so regardless of their characteristics, which is inconsistent with the fundamental premise of the CF that product, not process, should be the determining factor. The mere act of using certain rDNA methods triggers regulatory oversight and the requirement to submit a large (but undefined) body of information to the BRS in order to receive a determination of what types of additional requirements or requests for information may be imposed. Further emphasizing the process-based approach in practice, a number GE products have been exempted from regulatory requirements simply because and alternative process was used (Camacho et al., 2014). The fact that such a submission is required already constitutes "regulatory oversight" and a burden on users, regardless of any approvals that may subsequently be conferred. [And it is worth noting that all full petitions submitted to date have been approved, indicating that the process is essentially superfluous and expends enormous time and money to confirm that these products are fundamentally safe.] Numerous valuable crop products have been stymied from commercialization by the cost and uncertainty of this very first step that must be passed only by GE products (e.g., Driver et al., 2004; Horvath et al., 2012). In fact, we previously documented that between the period of 2003 and 2008, over 260 plant products representing 77 species of specialty crops utilizing GE methods had been described in the scientific literature or regulatory documents, nearly all of them conferring agriculturally

useful traits, but virtually none of which have been commercialized due to the hurdles imposed by the regulatory system (Miller and Bradford, 2010).

Scientific reviews have repeatedly reached the opinion that the process of genetic engineering itself does not create unique risks that are not also present in other types of genetic modification, such as wide crosses or mutation (e.g., NAS, 2004). Experience to date with the GE products that have been commercialized and produced on a large scale also does not indicate any unexpected issues from the techniques used. In fact, in contrast to often-repeated concerns about the stability of inserted genes, unanticipated and off-target effects, etc. (Rissler and Mellon, 1996), the actual experience is that the same transgenic events commercialized in 1996 are still stable and performing as expected 20 years after their introduction. The concerns have instead shifted to how to continue to allow use of some of those original events (e.g., glyphosate resistance) after the patents on them have expired (Jefferson et al., 2015). This concern is entirely based on the regulatory status of these events and the requirement in some countries to renew and sustain regulatory permits and licenses, which again are unique to GE products. Thus, it is not a lack of stability, function or safety of the GE traits themselves that creates risks, particularly marketing risks, but rather their status as "regulated articles" that can result in economic damage due to low level presence, market discrimination and import bans. It was originally a mistake and inconsistent with the CF guidelines to create a specific regulated category of products based solely on the methods used to create them, and it is time for the regulatory system to correct this error and put a system consistent with the CF guidelines in place.

I hasten to add that the conclusion that GE methods *per se* are no more risky than other breeding methods does not imply that all breeding using conventional methods should therefore also be regulated. For example, critics often claim that inadvertent mutations associated with transgenic methods could cause dangerous and unknown risks. However, over 2250 varieties of plants have been developed and commercialized over the past 50 years using induced mutation without a single safety issue (Ahloowalia et al., 2004). In these cases, plants have been heavily mutagenized, resulting in thousands of unknown mutations per plant, yet once selected for the trait of interest, no inadvertent toxicities or risks have ever been reported. Similar accumulated experience with other genetic modification methods (wide crosses, protoplast fusion, etc.) similarly demonstrates that the likelihood of unexpected consequences due to mutations that may be associated with genetic engineering is also extremely low (only three cases ever reported, and these were in programs attempting to increase pest resistance based on pre-existing known toxins). This further supports the tenet of the CF that it should be the trait itself and the product created, not the method used, that determines whether regulatory review and oversight are required. It also indicates that even extensive mutation and genetic modification do not result in unknown toxicities and allergens in crop plants, as is often proposed as a potential risk of genetic engineering. Extensive experience with diverse genetic modification techniques, as well as recent evidence of the much greater fluidity of genomes than was previously appreciated, suggest that truly risky consequences of genetic engineering in crop plants are exceedingly rare and thus should not be the basis of regulatory policy (Ladics et al., 2015).

These considerations are particularly critical now, as methods have become available that can very precisely target genetic modifications to specific locations in the genome (Joung and Sander, 2013; Pennesi, 2013). The application of these methods (zinc-finger nucleases, TALENS, CRISPR, etc.) enables site-specific gene transfer and DNA base modifications within target genes. This greatly reduces the

likelihood of off-target effects and further weakens any scientific rationale for regulating them in a more stringent way than mutagenesis. Again, given the long history of safe use and lack of evidence of unexpected effects from mutagenesis, and the ability now to make genetic changes with methods that greatly reduce the probability of unknown changes to orders of magnitude below that found in mutagenesis methods, there can be no rationale for including these so-called gene editing methods in a risk category that would require pre-market review or regulatory action for commercialization. Instead, they strengthen the original intent of the CF that it should be the product of the intended modification that determines whether pre-market review is justified. APHIS to date has reviewed products on a case-by-case basis, and has exempted a number from requiring regulatory oversight. This should be made a general rule for these gene editing techniques as long as the targeted change does not present any evident safety issue in the intended product. A straightforward explanation of the target gene, the modification made, and the consequent change in phenotype of the product should be sufficient for review to determine eligibility for such exemption.

Another consequence of removing the special regulatory status of GE products is that it would no longer be a "major regulatory action" by the government that has been the basis of numerous legal actions by groups opposed to biotechnology. The regulatory review and approval required from BRS has enabled such groups to distort the intent of the National Environmental Protection Act (NEPA), for example, and use it as a vehicle to file suits to prevent the release of GE crops. For example, both herbicide-tolerant alfalfa and sugar beets were delayed in commercial release for years through this approach and the BRS was required to conduct full Environmental Impact Statements, using years of BRS staff time, only to confirm what was already evident, that the products themselves constituted no plant pest risk. In contrast, the GE crops commercialized to date have been highly successful both economically and environmentally, increasing farm revenues and consumer benefits while decreasing fuel and pesticide use and environmental impacts of agricultural operations. These benefits have occurred without any documented adverse safety consequences for humans or the environment. Any market disruptions and economic losses associated with GE crops have occurred entirely as a result of regulating all GE products with zero tolerance policies that are unnecessary and unreasonably restrict their use and movement. The economic consequences of the flawed regulatory approach then become the basis for further litigation, none of which is based on the product itself, but rather on the irrational zero-tolerance thresholds for "regulated articles" that are the actual cause of market disruptions. If OSTP is serious about its goal of "reducing regulatory burdens and avoiding unjustifiably inhibiting innovation," as well as avoiding defending itself endlessly in court, then getting rid of its arbitrary process-based system would be the first step.

The current review should also reconsider APHIS current practice of exercising regulatory authority because it can, rather than because it is needed or improves public or environmental health or safety. For example, as a university researcher, I have been required to apply for a permit to mail a few transgenic tomato seeds to a colleague at a university in another state for strictly research purposes. If my colleague had been at a university in my own state, no permit would have been necessary. Why is there a greater risk of "environmental release" from one mailing compared to the other? What is APHIS' interest in whether I mailed these seeds or not? What fraction of these interstate notifications for research purposes has ever resulted in any actual release or any action by APHIS beyond the initial review and issuing of the permit? Why is APHIS spending resources and staff time in this activity at all, and requiring users to spend time preparing and submitting applications, for this extremely low risk activity? Transgenic

Arabidopsis seeds have been conditionally exempt from this permit requirement since 1990. Has this caused any problems? On the contrary, the ease with which transgenic stocks of Arabidopsis can be exchanged among researchers is critical to facilitating its use as a model scientific system. Why, then, are researchers working on any other plants handicapped by requiring them to obtain permits for something they can do routinely with a weed? I have previously discussed this point with APHIS staff at a Public Forum, and the only rationale I received was that they had authority to regulate interstate movement but not intrastate movement, so therefore they were regulating interstate movement. I received no answers to the questions above about the relevance and value of this activity to goals of preventing release of plant pests. In this instance, APHIS is regulating because it can, not because it needs to. I urge you in the current review to carefully consider the actual value of any proposed regulatory scheme in furthering its intended goals, as the risk of unintended consequences from regulatory actions is in fact greater than that from the release of GE crops, as the latter undergo extensive testing, trialing and selection prior to release, whereas regulatory actions are enacted without trial, and as the passage of 7 years from the last proposed (but subsequently abandoned) amendment of the BRS scheme demonstrates, seem to be impervious to subsequent selection, modification or change in light of experience.

In summary, the nearly 20 years of safe commercialization of GE plants indicates that the excess of caution initially embodied in the regulatory approach to them is unnecessary. It has, in fact, been the source of virtually all of the adverse economic impacts of GE crops through zero tolerance restrictions on trade and discrimination in the marketplace due solely to the process by which they were developed. While it is true that most of those impacts are due to regulations in other countries, the U.S. as the source of most innovations in crop improvement and whose farmers have benefitted most from them, should be leading in broadening their use. We cannot control the actions of other countries, but neither should their actions constrain us. Under the latter logic, the fact that China blocks its citizens from using Google would imply that we should also ban it, despite its broad value in the U.S. for education and commerce. Instead, the U.S. regulatory approach toward GE should build on our long experience and scientific leadership to eliminate most hurdles to commercialization and restrict regulatory reviews only to products for which there is a reasonably high probability of actual adverse consequences. In addition, the potential benefits of GE products should be explicitly considered in risk analyses, as preserving the status quo is often not to the benefit of the environment or the consumer. I urge you to adopt a fully scientific approach to risk assessment, which would result in removal of regulatory requirements for gene editing and transgenics *per se*, and would focus only on the characteristics of the products created by these methods, consistent with the original intent of the CF. In particular, any product that could be created using conventional breeding methods, including wide crosses and mutagenesis, regardless of the methods used in its production, should be automatically exempt from regulatory review. I appreciate this opportunity to comment on the needed revision of the regulatory system for products of Biotechnology in the U.S.

Sincerely,

Kent J. Bradford
Distinguished Professor
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