April 11, 2016

Comment on Docket No. APHIS-2014-0054-0023

I am writing with reference to Docket No. APHIS-2014-0054-0023 “Environmental Impact Statement; Introduction of the Products of Biotechnology.” I am a Distinguished Professor of Plant Sciences and Director of the Seed Biotechnology Center at the University of California, Davis. I am a specialist in seed biology, genetics and biotechnology have been engaged in scientific research and teaching associated with these topics for the past 34 years. I am submitting the following comments for consideration in connection with the proposed definition of “biotechnology” and the options for revision of the current structure of the regulations associated with products developed through the use of biotechnology in relation to the Coordinated Framework (CF) established in 1986 and revised in 1992. I will also provide specific recommendations that would enable the Biotechnology Regulatory Services to achieve its overall goals of ensuring “a high level of environmental protection pursuant to APHIS’ PPA authorities to regulate plant pest and noxious weeds, improve regulatory processes so that they are more transparent to stakeholders and the public, and provide regulatory relief to the extent possible so that unnecessary regulatory burdens are eliminated.”

To begin my comments, I include by reference here a paper published in 2005 specifically on the topic under consideration (Bradford et al., 2005) and a second paper documenting how the current biotechnology regulatory system is an impediment to the development and commercialization of products of biotechnology (Miller and Bradford, 2010). These negative consequences already were 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). As nothing has changed in the regulatory system since those papers were published, or in fact since even earlier similar analyses were published (Barton et al., 1997), everything in these papers remains fully relevant today. I also include here by reference my comments submitted November 9, 2015 to FDA-2015-N-3403-0001 (tracking number 1jz-8m5i-t05p) on closely related topics.

The definition of biotechnology proposed in connection with the current Docket is: “Laboratory-based techniques to create or modify a genome that result in a viable organism with intended altered phenotypes. Such techniques include, but are not limited to, deleting specific segments of the genome, adding segments to the genome, directed altering of the genome, creating additional genomes, or direct injection and cell fusion beyond the taxonomic family that overcomes natural physiological reproductive or recombination barriers.” I have several criticisms of this definition.

1) It is unclear why whether a process occurs in a laboratory or not should be relevant to whether the product is a plant pest or noxious weed. A primary principle of the CF was “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. Basing the definition of “biotechnology” as being “laboratory-based” immediately violates this principle by focusing on process. It would mean that genome modifications that do not require laboratory techniques, such as induction of haploid plants via wide crosses, are exempt from the definition, although the products might be identical to ones produced by techniques that do occur in a laboratory. What is the rationale, particularly the regulatory rationale, in which whether a process is laboratory-based or not becomes the primary criterion of whether it is to be termed “biotechnology” and therefore subject to unique regulatory attention? This definition in its very first words reveals that it is process-based, rather than being product-based as mandated in the CF but not applied in current biotechnology regulatory procedures.

2) The use of “intended altered phenotypes” is curious in this context. Does this imply that “unintended altered phenotypes” that resulted from the same processes would not be considered to be products of biotechnology? Or is it subtly implying that “intended” alterations are in some way different from “random” or “natural” alterations? If an unintended alteration happened to be beneficial or useful (as has occurred using mutagenesis), would it not be covered by this definition?

3) At what point in the process of altering a genome is “laboratory-based” relevant? For example, molecular (DNA-based) markers that have become standard components of the breeding process are assayed in the laboratory. Since such markers are used for “directed altering of the genome” by identifying specific organisms for selection following recombination, they would seem to fall under the definition. (See comments below about the proposed exception to the definition for marker-assisted breeding.)

4) Use of the phrase “Such techniques include, but are not limited to” leaves it vague what additional techniques not mentioned might also be included in the definition. A major problem in current regulatory practice is the uncertainty it creates for developers of new products as to whether such products are subject to special regulation and if so, what data or evidence might be required in the regulatory process. This open-ended phrase continues that uncertainty.

5) On what basis is the taxonomic family considered to be a significant limit for the use of genetic diversity? As our knowledge of the relatedness and evolution of organisms improves, taxonomic relationships are often adjusted, grouped or split. Furthermore, it has become evident from genomic studies that large fractions of genomes are shared far beyond the family level. Is it possible, therefore, to assign unique risks to genes that may be virtually identical across essentially all plants, for example, relative to differences among genera or species that might actually confer quite distinct properties? A purely science-based analysis might predict greater phenotypic change from the latter relative to the former. As our understanding of the genome increases, our appreciation of its generality and fluidity also increases (Ladics et al., 2015), revealing taxonomic limits as proposed here to be politically rather than biologically based.

6) Similar considerations apply to whether a product was developed by a process that “overcomes natural physiological reproductive or recombination barriers.” Why should “naturalness” *per se* be a criterion of risk? Some of the most potent toxins known are natural products, so “naturalness” does not in itself guarantee safety. Plants lacking natural reproductive barriers between them could also present risks. For example,
rapeseed and its derived modern variant canola are completely interfertile, and the capacity for production of toxic erucic acid from rapeseed could be transferred to canola through a natural process. On the other hand, plant breeders have long overcome natural reproductive barriers by various methods (e.g., embryo rescue) and many useful and safe cultivars have resulted. Similarly, overcoming recombination barriers is in fact an advantage, as it allows the elimination of unwanted genomic regions and retention of desired traits following such crosses. Why would we want to restrict or tightly regulate such useful and beneficial methods and processes?

Following this problematic definition of “biotechnology,” the background document states, “This definition does not include and is intended not to include traditional breeding, marker assisted breeding, or chemical or radiation-based mutagenesis.” This statement is both false and problematic. It is false, as in fact the definition clearly does include methods that are considered to be included in “traditional breeding”, such as wide crosses and embryo rescue which overcome natural reproductive barriers, require laboratory-based methods and result in intended altered phenotypes. There can hardly be a more “direct altering of the genome” than mutagenesis, which in this final sentence is exempted from the definition that would clearly include it. The fact that over 2250 plant cultivars have been developed using mutagenesis without any evidence of increased risk or lowered safety is a valid basis for this exemption, but the need for such an exemption simply reinforces the internal contradictions in this process-based definition.

Further, this exclusion statement is problematic because it indicates that despite the definition given, some processes clearly included in it are in practice exempted. Why specifically these methods and not others? What processes are included in “traditional” breeding? Marker-assisted breeding is clearly captured by this broad definition but is specifically exempted. How will a practitioner know whether a specific process being employed is considered to be among those that are exempted? Intentional mutagenesis has only been practiced actively for 60 years or so, and is known to result in thousands of unintended DNA base changes, yet is exempted. 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 DNA base modifications and gene replacements. 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. How long will it take for such practices currently covered by the definition of biotechnology to become “traditional” and therefore exempted? Even though such an exemption is subsequently proposed in the current document (see below), to create a broad definition and then state that it does not include what it clearly does encompass is arbitrary and confusing.

While recognizing that APHIS is mandated to develop and administer a regulatory system for products of biotechnology, the problems described above illustrate why approaching this task from a process basis is illogical, unscientific and a poor foundation for regulation. The original analysis and conclusion of the CF was correct on this point, that it should be the product and its properties, not the process by which it was developed, that should be the basis for its evaluation. If APHIS is serious about revising and updating the biotechnology regulatory process, reinstating
and actually incorporating this central tenet of the CF should be the top priority. This concept will guide my comments on the four alternatives that are proposed in the background document.

First Alternative. As a “no action” alternative, this is clearly unacceptable. I refer back to the prior publications and comments mentioned above for why change in the regulatory process is long overdue.

Second Alternative. Conceptually, the change to a “review first, regulate only when necessary” process would be an advance over current practice. The second part, “regulate only when necessary,” seems self-evident and consistent with the charge to “provide regulatory relief to the extent possible so that unnecessary regulatory burdens are eliminated.” The issue then is what does it mean to “review first” and what process is involved in securing such review. It is somewhat confusing that the proposal would retain an apparent requirement to submit to such a review, yet says that the current petition process for non-regulated status would be eliminated. It is critical to know what would be involved in the new review process and how it would differ from the current petition process. If the review process involved only addressing whether it met the stated criteria and a description of the phenotype, then it would be a very positive development. If the review process required essentially the same extent of data submission that is required for a petition, then it is not really a significant change.

A truly significant change would be to adopt the stance that is taken toward traditional breeding, as demonstrated by exception of those methods from regulation. That stance is essentially “innocent until proven guilty.” That is, no regulatory review, notification or permit is required to release a new plant developed by traditional means. This is justified by the long history of genetic crop improvement with only two or three cases ever in which any safety problem was identified. With such a low probability of risk, it is rightly concluded that the assumption of safety is justified and pre-market regulation would be considered excessive and burdensome. The background document states that, “the Coordinated Framework has consistently held and proceeded pursuant to the concept and position that the process of genetic modification has not been shown to be inherently dangerous.” If that is the case, why should a presumption of risk and danger be inherent in the agency’s regulatory approach to biotechnology?

With respect to the two specific criteria that would trigger review, the first includes that they are a plant, so clearly all new crop varieties developed using biotechnology would meet that requirement. The second is “Whether the product of biotechnology’s donor or recipient organism, or the vector used in its development meet the definition of a plant pest, is included in the list of plant pest taxa, or is unknown or unclassified.” While specifically addressing APHIS’ plant pest responsibility, this in fact captures some very low risk products and does not capture others. By including vectors derived from possible plant pests, this would continue to capture for review Agrobacterium-based transformation products solely because the vector used was derived from that organism, even though all of its “plant pest” functionality has been removed. Similarly, viral or bacterial gene promoters (e.g., 35S) would be captured even though their use per se would have little or nothing to do with whether the product had a trait that might warrant regulation. At the same time, it exempts very similar or identical products if they do not use those specific tools and vectors (Camacho et al., 2014). All this does is drive developers into the use of less efficient and less precise methods simply to avoid regulatory burdens. Again, this
process-based approach is fundamentally flawed and should be abandoned. Retaining it as the key criterion for determining whether review is required preserves the worst characteristics of the current regulatory scheme while doing little to predict or prevent actual risk.

APHIS asks for comment on other possible regulatory review criteria. One response would be to ask what criteria APHIS uses in its assessments of potential plant pests that are not related to biotechnology. In general, domesticated crops are not considered to be plant pests. Hundreds of traits, including for example disease resistance traits, have been transferred to and among crop plants by traditional breeding and there have been no reports of any of them becoming pests or causing environmental damage due to the incorporation of such traits. However, transfer of disease resistance traits via biotechnology under the current system triggers extensive data requirements, environmental assessments, etc., simply because of the method of transfer to the crop. Given the very extensive history of success of genetic transfer and release of disease resistance genes in crops, including from wild relatives that might in themselves be considered as potential pests, why should direct transfer via biotechnology methods trigger special consideration? Again, given the historical precedent, it would seem that the presumption of innocence would be fully justified regardless of the process involved and no prior review would be required.

This is a clear example connected to the APHIS’ request for “public input on potential justifiable exceptions or exemptions that would exclude certain “products of biotechnology” from APHIS’ regulatory review and oversight because they lack the realistic potential to pose documented plant pest or noxious weed risks.” In this section, APHIS proposes to exempt products of biotechnology that “could reasonably be expected to be obtained through mutagenic techniques.” Based on the foregoing discussion, this is an obvious example of superfluous regulation.

However, the approach of first capturing and then specifically exempting this application of biotechnology illustrates that fundamentally, this is a “regulate first, exempt later” approach. That is, rather than accepting the scientific fact that it does not matter how specific changes in DNA are accomplished, the process distinction is maintained and then some applications are selectively exempted. This underlying arbitrariness of the Second Alternative is inconsistent with the product-based focus stated in the CF.

The proposed elimination of the current notification process is a positive aspect of this Alternative (see also my comments to FDA-2015-N-3403-0001 for more on this). The elimination of the petition for non-regulated status process would also be positive, if the pre-market review process that replaces it is in fact science-based and rational and is only required for products that express traits that have a high expectation for creating risks. It may still be appropriate for APHIS to require notification of intent to release products of biotechnology, including a description of the gene(s) and processes used and the resulting traits as expressed in the plant phenotype. In the vast majority of cases, this should be sufficient to allow determination of whether a plant pest risk is present in comparison to similar products of traditional breeding. If the risk is comparable, there would be no further involvement of APHIS in its commercialization. If a potential risk was identified, further review and analysis could be requested/required. I note that to date, no petitions for non-regulated status of biotechnology products have been denied for cause, despite ever-increasing data request burdens, broadening criteria and full Environmental Impact Statements. Thus, the record to date supports moving
from a presumption of guilt to a presumption of innocence standard. As is the case for the FDA’s regulation of food safety, APHIS would retain authority to act to impose regulatory requirements on production or remove a product from production should evidence of harm appear. While critics may suggest that this would be too late in the case of plant releases due to potential escape or outcrossing, farmers routinely change varieties within a crop and past varieties do not become pests. In addition, 98% of the food crops grown in the US are introduced species that do not have close relatives in the wild (Juma, 1989), meaning that the potential for outcrossing to related wild relatives is present in only a few species.

**Third Alternative.** This alternative to increase regulatory oversight and require permits for any application of biotechnology is evidently inconsistent with the facts. After the enormous effort expended over the past 30 years on regulatory review and oversight, and the associated stifling of the advances that biotechnology has to offer for both agriculture and its sustainability, and still not finding a single proposed product as being of sufficient risk to block its commercialization, what possible rationale could there be for this option?

**Fourth Alternative.** At last, a proposed alternative that would be consistent with actual practice and experience and with the principles of the CF. While perhaps considered to be oxymoronic that a regulatory agency would cease to regulate, this is in fact what should be done. As proposed under the Second Alternative, APHIS believes that many genetic improvement methods do not require regulation and therefore receive a blanket exemption from regulation, and such exemption is not considered to be incompatible with its mandate to control plant pests. In a product-based approach, this same assumption of safety would extend to products having similar types of traits regardless of how they were introduced. Thus, only truly novel traits would likely be subject to deeper review and analysis. The voluntary consultative process proposed would essentially be the pre-market abbreviated review mentioned above. Even if consultation were mandatory, the role of APHIS in most cases would be advisory, as proposed here, but would serve to catch any products that might actually have unforeseen risks that APHIS’ experience and authority would be able to prevent or mitigate. However, as for FDA regulation of food, the developers/marketers, not APHIS, are ultimately responsible for the safety and performance of the products they release. While possibly viewed as radical from the perspective of the unnecessary over-regulation in the current system, this in fact is the alternative most consistent with the principles in the CF and with the evidence to date with products of biotechnology, both those that have been commercialized and those whose commercialization has been blocked by the current excessive regulatory burden (Miller and Bradford, 2010).

Another important consequence of removing the special regulatory status of products of biotechnology is that such regulation 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 governmental regulatory review and approval required 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 such crops. Both herbicide-tolerant alfalfa and sugar beets were delayed in commercial release for years through this approach and APHIS was required to conduct full Environmental Impact Statements, using years of staff time, only to confirm what was already evident, that the products themselves constituted no plant pest risk. Any market disruptions and economic losses associated with biotech crops have occurred
entirely as a result of the fact that they are regulated in some jurisdictions with zero tolerance policies that unnecessarily 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 effects of the irrational zero-tolerance thresholds for “regulated articles” that are the actual cause of market disruptions. IfAPHIS is serious about its goals to “improve regulatory processes so that they are more transparent to stakeholders and the public, and provide regulatory relief to the extent possible so that unnecessary regulatory burdens are eliminated,” as well as avoiding defending itself endlessly in court, then abandoning its arbitrary process-based system would be the first step.

In summary, the 20 years of safe commercialization of plants improved through biotechnology demonstrates that the excess of caution initially embodied in the regulatory approach to them is unnecessary. Regulation itself has, in fact, been the source of virtually all of the adverse economic impacts of such crops through creating a special regulatory category for them that allows 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, as the source of most innovations in crop improvement and whose farmers have benefitted most from them, the U.S. should be leading in broadening their use and reducing regulatory impediments. 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 biotechnology 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 reasonable possibility of actual adverse consequences. In addition, the potential benefits of products improved through biotechnology should be explicitly considered in risk analyses, as preserving the status quo is often not to the benefit of the environment or the consumer. APHIS has the opportunity and responsibility 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 proposed Environmental Impact Statement associated with revision of the regulatory system for products of Biotechnology in the U.S. I would be glad to provide further background on or documentation of any statements in this comment.

Sincerely,

Kent J. Bradford
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References cited


