The proposed APHIS regulation modernization could enhance agriculture biotechnology research and development in the USA

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Abstract

The USDA's Animal and Plant Health Inspection Service (APHIS) is one of three agencies that govern the importation, interstate movement, or environmental release of certain genetically engineered (GE) organisms. APHIS regulations are in 7 CFR part 340, originally issued in 1987 (https://www.aphis.usda.gov/biotechnology/downloads/7_cfr_340.pdf) and based on the premise that a GE crop could pose a plant pest risk. A major revision was proposed June 6, 2019 (https://www.aphis.usda.gov/brs/fedregister/BRS_20190606.pdf), with public comments accepted for 60 d. Members of the Society for *In Vitro* Biology (SIVB)—especially within the plant section—are impacted by the current rules and will be impacted by changes. Therefore, the public policy committee studied the changes and prepared a response that was reviewed by the board of directors and submitted to APHIS. APHIS received 6186 comments overall. In general, the SIVB welcomes the proposed revisions, which recognize established scientific guidelines and principles for plant pest risk assessment. In addition, they recognize the safety record accumulated over multiple decades of current GE mechanisms of action (MOA), so the proposed rules include an exemption for new events with established MOA's in a previously reviewed crop. Further, the proposed rules focus on DNA function and impact rather than its source organism with regulatory review triggered by potential for increased plant pest risk. Most importantly, the proposed revisions codify a light regulatory approach for many applications of genome editing, because these applications result in plants that could otherwise have been developed through traditional breeding techniques or found in nature. If implemented appropriately in the final rule, we find these changes remove many current barriers, and thus are likely to stimulate university and business “startup” innovation. The SIVB recognizes the need for exemption for further model species and gene delivery organisms. Such concerns were adequately expressed by the submitted response. Remaining hurdles for innovative plant incorporated protectants are still problematic. Nevertheless, the SIVB applauds the efforts to update APHIS rules in a scientifically defensible manner. The detailed response is shared below.

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Abbreviations

AIR	Am I Regulated
APHIS	Animal and Plant Health Inspection Service
bp	Base pair
CFR	Code of Federal Regulations
DNA	Deoxyribonucleic acid
EPA	Environmental Protection Agency
EPSPS	5-enolpyruvylshikimate-3-phosphate synthase
FDA	Food and Drug Administration
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
GE	Genetically Engineered
ISAAA	International Service for the Acquisition of Agri-biotech Applications
MOA	Mechanism of Action
PIP	Plant Incorporated Protectant
PMPI	Plant-Made Pharmaceuticals and Industrials
PPA	Plant Protection Act
SIVB	Society for In Vitro Biology
SNP	Single Nucleotide Polymorphism
tRNA	Transfer Ribonucleic Acid
TSCA	Toxic Substances Control Act
USDA	United States Department of Agriculture

Introduction

The Society for *In Vitro* Biology (SIVB) is a professional society devoted to fostering the exchange of knowledge of *in vitro* biology of cells, tissues, and organs from both plant and animals (including humans). The focus is on biological research, development, and applications of significance to science and society. The SIVB membership is composed of academics ranging from professors to students, industry members, and other interested expert members that work in the area of tissue culture and other biotechnologies. SIVB members have played leading roles in the development, safety evaluation, and deployment of genetically engineered organisms, and these members also tackle similar issues in gene editing.

We have come to understand the plant genome in far more depth than could even be dreamed about when the original CFR 7 part 340 was first adopted over three decades ago. Even though our understanding of the plant genome remains incomplete, it is now amply evident that most of the agricultural concerns related to the use of recombinant DNA in crop plants do not have a strong biological underpinning, as has been borne out by experimental and real-world experience (<http://nassites.org/ge-crops/2016/05/17/report/>). The experience from the past quarter century, during which a cumulative total of 5.3 billion acres (an area 2.8× the size of the continental USA) had been planted in GE crops by 2017, (ISAAA.org), also makes it clear that the possibility of unreasonable harm from a GE crop was also greatly overestimated in the 1980s.

Therefore, the SIVB applauds the efforts by APHIS to modernize its regulations. While it is unfortunate that the proposed changes do not completely get away from a regulatory trigger based on the process used for modification, they are an improvement and have a stronger scientific foundation than the current part 340 does. These changes also acknowledge that not all risks are created equal and can thus be handled based on the level of risk they pose. Finally, the proposed reforms do a good job of balancing the needs of the developers with the realities of the market place. Accordingly, the SIVB is pleased to provide comments as requested by APHIS.

Comments to APHIS

1. In the revised part 340, plant pest risk is being defined as “[t]he possibility of harm resulting from introducing, disseminating, or exacerbating the impact of a plant pest.” SIVB finds the term ‘harm’ to be inappropriate in this context because the term is too subjective, with any agricultural activity having the potential to cause some type of harm. More appropriate (and defined) terms are used in other legislation regulating agricultural activities, *e.g.*, ‘unreasonable adverse effects’ in FIFRA (section 408 of the Federal Food, Drug, and Cosmetic Act). Application of this concept in this context would require unreasonable adverse effects resulting from a trait introduced to a crop by recombinant DNA and not resulting from some other pre-existing characteristic of the crop.
2. The current paradigm of evaluating each individual insertion of transgenes, even of the same transgene in different individuals (different “events”) of the same crop, comes from a 1980s concept that each DNA insertion occurs at a different location, and this could impact on plant physiology and biochemistry. While this concern is technically plausible, the probability of adverse effects is too low to be measurable. This conclusion is based on the fact that the plant genome is naturally highly plastic, undergoing reorganizations that involve far more insertions (Weber *et al.* 2012; Schnell *et al.* 2015) than the process of genetic engineering can cause, and this occurs frequently without adverse impacts to agroecosystems. Therefore, APHIS has a solid scientific footing upon which to abandon its event-by-event regulation of the same or substantially the same gene in the same crop. Yet, by retaining an optional review by the developer (§ 340.1(d)), developers can still address market place requirements. As proposed, the new rule still provides APHIS with the necessary flexibility to evaluate new gene-crop combinations for which less is known.
3. Under § 340.1(b) of the proposed rule, APHIS will be able to exempt certain categories of modified plants, if

they can be recreated using traditional techniques. Because risk is derived from the traits modified and not the way the trait is modified, and because traditional breeding over the past century has an exceptional safety record, APHIS is on firm scientific footing with § 340.1(b) of the proposed rule.

4. Under § 340.1(c) of the proposed rule, APHIS would exempt GE plants with plant-trait-mechanism of action (MOA) combinations that already have been evaluated. Again, APHIS is on solid footing with this proposal. The reason is that many organisms share the same gene, having been inherited from a common ancestor. For example, several safety evaluations have been performed on the EPSPS gene from *Agrobacterium* spp. However, all plants and bacteria have their own version of these genes. As reviewed (Hammond *et al.* 2013), there has been no reported evidence that some orthologs of this gene are more likely to lead to adverse effects than others, as long as the overall gene family is not associated with toxins or allergens. Based on evolutionary history and on the experience from direct gene evolution, large proportions of the amino acids in an enzyme may be substituted without altering protein innocuity. Thus, the MOA is an elegant, scientifically sound criterion to use.
5. APHIS notes: “We would note here that a developer making a self-determination that APHIS determines not to be valid may be subject to remedial measures or penalties in accordance with the compliance and enforcement provisions, which are discussed below, in proposed § 340.6(c) if the organism is moved without proper authorization under part 340. In addition, penalties and remedial measures (including but not limited to, quarantine, seizure and/or destruction) under the authority of the PPA may be exercised.”

First, SIVB agrees that self-determination is appropriate for the categories listed by APHIS. The principle behind self-determination is similar to how FDA operates—there is a requirement that any food placed in the market place is safe, but suppliers do not need to run every ingredient or food product past FDA unless they have a question. Such a voluntary consultation system has functioned very well, and there is no reason why self-determination cannot work equally well for APHIS.

Nevertheless, this APHIS statement introduces a measure of ambiguity into the ability to self-determine. While penalties for violators are appropriate, penalties for an event honestly but incorrectly self-determined to be exempt when it is not can serve as a deterrent to self-determination, particularly if the event is one with no or very limited potential to cause harm. The ambiguity is a disincentive to self-determine and could lead to the voluntary requirement becoming a *de facto* requirement.

Therefore, APHIS needs to elaborate on this statement, so that developers are not left with the current uncertainty that a self-determination could lead to bankruptcy—inducing potential compliance infractions and penalties. Clarity for developers is crucial for having a viable and effective regulatory scheme.

A single, fixed size penalty is simply a disincentive. APHIS should be explicit that it will invoke the compliance and enforcement provisions against developers making a self-determination that APHIS considers incorrect only if APHIS determines that the inaccurate self-determination caused actual harm. APHIS should use its regulatory discretion regarding compliance and enforcement powers so that APHIS invokes these powers only when the misclassification causes an actual harm. Therefore, APHIS should invite further comments on potential threshold levels of harm and the penalties they would warrant.

6. APHIS asks: “We are requesting comments from the public, however, on whether the scope of the regulatory status review should be expanded to include non-plant GE organisms as well as GE plants, whether some equivalent process for evaluating such organisms for regulatory status should be developed instead, and, if so, what factors the Agency should consider in its analyses.”

There is no reason why plants should be set aside for special treatment. All organisms should be evaluated according to the same standards. Many non-plant, modified organisms are already regulated under the auspices of other regulatory bodies (EPA or FDA). Additional consultations between APHIS and EPA/FDA to better define who will regulate other organisms is warranted. Often determination of the responsible agency depends on the intended use for the genetically modified organism. SIVB recommends harmonizing these regulations as they apply to agricultural use to avoid creating redundancies or complications that come from different agencies with overlapping jurisdictions. Furthermore, any such regulations should be scientifically valid and target real, not contrived risks. Such regulations should also be proportional to the risk, if any risk is present.

7. SIVB notes and commends APHIS for the added flexibility a developer will have for new plant-MOA combinations that are not otherwise exempt. A developer who initially requests a permit would also have the option of following up with a request for a regulatory status review. Previously, requesting a permit was a one-way street. The ability to request a permit and then request regulatory review status will undoubtedly incentivize and accelerate new product development.

However, if it does become necessary for a developer to request a permit, there is no time frame for this “regulatory review” process. The current petition process has a time frame. Though this time frame is rarely followed, it

provides a goal for the agency to act in a timely manner. Thus, a time frame should also be included in the newly revised regulations, *e.g.*, 360 d.

8. APHIS asks: “Agency is aware of the implications of this rule with regard to PMPIs, and to request specific public comment regarding the best manner to address this issue.”

The SIVB urges APHIS to adopt a clear risk-based analysis for its treatment of PMPIs. APHIS should not let fears of “contamination” create regulatory barriers. As a first step, APHIS needs to acknowledge that not all pharmaceuticals and industrial compounds are a hazard (Conko *et al.* 2016). APHIS should look towards science in a risk-based approach. For example, humans routinely and safely consume antibodies with every glass of milk they drink or meat or egg they eat. In fact, the colostrum considered so important for newborns is laden with antibodies. Likewise, people who need growth hormones or other biologicals must have them injected because they are digested and therefore, ineffective, if ingested orally.

Many other PMPIs are probably innocuous but have not been assessed for safety. If they are reviewed by the FDA and found to be safe if ingested orally (because they are highly digestible and not allergenic or toxic), there is no reason for APHIS to impose further restrictions from a safety standpoint. Until then, they can be grown under permit.

Finally, there will be a category where there is an expectation of unreasonable adverse effects from ingestion of an orally active PMPI. For these cases or when safety has not been demonstrated, restrictions to planting may be appropriate. In all cases, these restrictions need to be congruent with the standard of “reasonable safeguards” set forth in the Coordinated Framework.

7 CFR part 360 is not an appropriate authority to use for PMPIs because the premise behind noxious weeds is to eliminate them, not control their production. Therefore, we suggest that PMPI status should require specific case-by-case regulation. Once risks are properly and clearly identified, APHIS then could think in terms of specific actions that address those risks so as to avoid “unreasonable adverse effects,” which is the criterion set forth in the Coordinated Framework. For example, APHIS could adopt tolerance levels or isolation distances or other practical, scientific-based standards and best management practices.

APHIS could also establish an education program to raise awareness of the need to exercise good stewardship practices for PMPI production to prevent escape, adverse public opinion, and subsequent liability.

9. APHIS asks: “the Agency is aware of the implications of this rule with regard to small-scale testing of PIPs and to request specific public comment regarding the best manner to address this issue.”

Unless a new plant-trait-MOA combination is involved, oversight for small (< 10 acre) field trials of PIPs will pass from APHIS to EPA, which could then require experimental use permits. EPA regulation of PIPs has greatly limited the use of GE for plant disease management, and thus continues to promote the use of chemical control agents. Simply put, the PIP concept is not fit for purpose, as described by Conko *et al.* (2016):

The EPA’s PIP concept is too artificial and contrived to have any relevance, beyond indicating that non-target species need to be considered during risk evaluation.

The lack of utility of the PIP classification is most evident in virus-resistant plants obtained using a gene(s) from the viruses that otherwise infect them, or when *cis* genes are used that could otherwise have been crossed in. There is simply no justification in data or experience for a regulatory classification of a PIP that singles out certain events for the same regulatory approach as if they were pesticides sprayed on crops. Our opinion is that this classification should be eliminated.

Therefore, as APHIS and EPA negotiate a new procedure for PIPs, EPA can be encouraged to discontinue the PIP concept. Instead, whether by APHIS or by EPA, efforts need to focus on measures to protect non-target species and on resistance management in those cases where a public good is involved. Resistance management is not required when resistance is introduced *via* breeding, so similar resistance genes should not be singled out if they are engineered or edited.

10. APHIS asks: “APHIS requests comment from the public regarding the categories of plants listed under proposed § 340.1 as not subject to the regulations, including their breadth, whether we need to provide greater specificity in the exemptions, and whether additional categories should also be considered for exemption from the requirements of part 340.”

The SIVB agrees with the APHIS rationale here. The experience of conventional breeding over the past century, as pointed out by the referenced academy reports, provides solid scientific support for the APHIS position. The description provided by APHIS is sufficiently clear that more specific examples are not needed. Nevertheless, providing a list together with the proposed regulations would provide the public with an opportunity to evaluate and comment on the list and be able to provide comments on APHIS’ list and others for either inclusion or exclusion.

The list of approved plant-trait-MOA combinations will be very useful to both private and public developers. Including “Am I regulated?” items is also warranted, given the lack of issues that have materialized from

these. For that matter, there is no reason why APHIS should not use these to determine regulatory status based on MOA, so SIVB urges APHIS not to exclude AIR plants for the list of approved plant-trait-MOA combinations.

SIVB disagrees with the second criterion, namely the limit of a one base pair substitution. A 1-bp substitution needs to be the starting point, not the ending point! Many alleles clearly differ by single base pair substitutions. While the odds of naturally getting two base pair substitutions in an allele is less frequent, it is not rare. An example is the *lc* gene for locule number, and hence fruit size, in tomato, which contains two causal SNPs relative to the wild-type allele (Muños *et al.* 2011). To further illustrate the point (Tenaillon *et al.* 2001), any corn protein 300–400 amino acids long from two alleles will differ by 3.5 amino acids. Since each amino acid change reflects a non-synonymous base pair change, each gene of this size in corn must differ from the same gene in another genotype by at least three naturally occurring SNPs!

More generally, average pairwise diversity is the standard metric for diversity. Even low-diversity species like soybean have average pairwise diversity of $\sim 1.6 \times 10^{-3}$ (Valliyodan *et al.* 2016). Therefore, any two lines will differ at every 800 bp. Thus, for a gene ~ 5000 bp in size, there will be roughly six SNPs between the alleles for this gene in any two lines.

Therefore, the limit to base pair substitutions needs to be removed, keeping in mind that too many nonsynonymous substitutions can render a gene non-functional and that there are no known instances of a harmless protein being converted into a toxin by replacing a couple of amino acids (Hammond *et al.* 2013).

There should be no limits to the number of synonymous base pair substitutions, as these do not change the amino acid sequence of any resulting peptide. Furthermore, many synonymous base pair substitutions may intentionally be created in order to optimize the codon matching to tRNA abundance in a given species, as this can optimize translation without altering the amino acid sequence.

The third criterion has to do with “modification [that] is solely introducing nucleic acid sequences from within the plant’s natural gene pool or from editing of nucleic acid sequences in a plant to correspond to a sequence known to occur in that plant’s natural gene pool.”

That criterion fails to consider the natural biology of double-stranded break repair. We note that the insertion of a few to several random bp of DNA is common following the normal repair of a double-stranded break (Wicker *et al.* 2010), as occurs during genome editing to knock out genes. Therefore, the presence of these

extra base pairs must not be a regulatory trigger. Accordingly, ‘Changes induced by cellular DNA repair mechanisms’ should be added to the list of changes not subject to regulations.

Alternatively, 7 CFR § 66.1 for labeling bioengineered foods contains a useful standard, “modification [that] could not otherwise be obtained through conventional breeding or found in nature.” The ‘or’ applies to ‘could not otherwise.’ Thus, ‘Could not otherwise be found in nature’ is an appropriate delimiter for changes subject to regulation. Using this criterion would have the added benefit of synchronizing the § 66.1 regulations with § 340.

Likewise, the concept of a ‘natural’ gene pool is not a biological definition. Accordingly, Harlan and de Wet (1971) proposed the concept of primary, secondary, and tertiary gene pools to classify the germplasm that conventional breeders have used historically. The tertiary gene pool is the one that requires extraordinary but conventional measures, such as embryo rescue or protoplast fusion. Since then, the use of recombinant DNA technology has provided access to genes beyond the tertiary gene pool, sometimes referred to as the quaternary gene pool.

Hence, ‘natural gene pool’ should be defined as ‘within the primary, secondary and tertiary gene pools’ or ‘genes that can be accessed without using recombinant DNA.’

11. APHIS asks: “APHIS requests comment from the public regarding the categories of GE organisms listed under proposed § 340.2 as subject to the regulations and whether additional categories, such as pollinators, should also be considered.”

APHIS has listed four categories of organisms that would require permits for movement in § 340.2. SIVB finds these categories to be logical and reasonable. Plants (we assume APHIS means plant-trait-MOA combinations, but their meaning of GE plant needs further clarification here) would be permitted under § 340.2(a). Again, this is not an unreasonable requirement.

SIVB commends APHIS for dropping the use or presence of plant-pest-derived DNA as the regulatory trigger. This criterion has had no basis in science whatsoever, and its dismissal is long overdue. The same goes for using *Agrobacterium* as the means to deliver DNA.

In § 340.2(c), APHIS lays out a logical and coherent approach to the regulation of non-plant GE organisms, such as soil bacteria. It is important to note that GE single-celled organisms are already regulated by EPA under TSCA or FIFRA, depending on their intended

use. It is essential for APHIS and EPA coordinate so as to prevent a duplicate regulatory burden.

12. APHIS is proposing to replace its current definition of genetic engineering with a new one, namely “techniques that use recombinant or synthetic nucleic acids to modify or create a genome.” SIVB finds this definition to be inadequate because it encompasses genome editing technology used to create deletions or used to replace one allele with another (*i.e.*, used to replace backcrossing in conventional breeding), which yield the same results as excluded techniques do. SIVB therefore requests a specific exemption for these two editing uses in its definition of genetic engineering.

The SIVB agrees with all the other proposed definition changes.

13. Under § 340.4(a)(4), APHIS describes the information needed to review the plant pest status of a new plant-trait-MOA combination. One such piece of information is “The genotype of the modified plant, including a detailed description of the differences in genotype between the modified and unmodified plant.” APHIS must limit the scope of genotypic changes to get away from the whole genome, as plant genomes are plastic and never remain unchanged. Case in point, a base pair substitution can be expected to occur spontaneously for every billion base pairs in the genome, excluding transposon movement and other changes (Weber *et al.* 2012). Thus, the scope of the requested information needs to be limited to the intentional genetic modification made.

SIVB agrees with APHIS that field data rarely contribute useful information for a risk evaluation. Therefore, SIVB agrees with APHIS that most assessments can and should be made without field data. Overall SIVB agrees with APHIS that the data requirements are consistent with the evaluation being conducted.

Given the large number of plant trait MOA combinations that would receive *a priori* exclusions from APHIS regulations, SIVB agrees that the current notification process can be abandoned in favor of a permitting process.

Paragraph of § 340.5(c) would continue to exempt stable GE Arabidopsis that does not have the complete genome of a plant pest. This exemption has greatly facilitated progress in plant molecular biology research in multiple universities without any adverse effects. Therefore, SIVB agrees with the wisdom of continuing this exemption. As an additional note, SIVB believes that any risks associated with the movement of GE Arabidopsis are immeasurably low, and there is no scientifically valid reason to justify “secure shipment.”

In § 340.5(d), APHIS also extends its exemption to disarmed strains of *Agrobacterium tumefaciens*. SIVB agrees with this action for all the reasons stated by APHIS. However, the taxonomic status of this bacterium is in flux, being also called *Rhizobium radiobacter* (<https://www.uniprot.org/taxonomy/358>). In addition, disarmed versions of *Agrobacterium rhizogenes* have an equally useful and safe record for transformation as do disarmed versions of *A. tumefaciens*. Therefore, SIVB requests that ‘disarmed *Agrobacterium tumefaciens*’ be replaced with ‘disarmed *Agrobacterium* strains’, or better yet, ‘disarmed members of the Rhizobiales’ such as *Ochrobactrum haywardense*.

Using the same reasons and arguments, APHIS should consider exempting *Nicotiana benthamiana*.

After Arabidopsis, ‘benthi’ may be the most useful non-crop model species for plant genetics research.

Along those lines, disarmed viruses are commonly used in plant molecular biology studies. Thus, why not just exempt any pathogen with the pathogenicity demonstrably removed?

The remainder of the terms and conditions for permit issuance are essentially as currently exercised. They are strict, striving towards zero risk, as opposed to the Coordinated Framework of criterion of unreasonable risk. It is important to maintain measures commensurate to risk—defining the risk hypothesis involved may help determine appropriate permit conditions.

A key difference from current regulations is that the time frames for permit issuance by the agency have been removed. This is a major issue for those who will be regulated, as the regulated community needs some certainty in terms of how long it takes to get a permit. They should absolutely include a time frame for permit issuance.

Also, there does not seem to be any language in the regulations regarding exactly when the multitude of reports for permitted planting will be due to the agency. As developers move forward in making planting plans, this introduces more uncertainty into when and how they will be required to comply with the regulations. There needs to be some reasonable time frames included in the regulations so that developers can plan ahead to stay in compliance.

Otherwise, SIVB is especially pleased to see that permits for multiple years will be available, as this action will relieve researchers from the bureaucratic burden of requesting the same permit over and over.

14. APHIS asks: “The Agency requests specific public comment regarding whether a shorter duration is warranted for certain records pertaining to permit activities and which activities these may be. Additionally, APHIS requests comment on any alternate means that stakeholders may identify for the Agency to obtain necessary information

from developers in the event of a fact finding or an investigation of possible regulatory noncompliance.”

In § 340.6(b), APHIS is proposing that records be maintained for 5 y, if not longer. Five years is commensurate with the length of time other types of records are stored. Thus, record retention should not be an undue burden, as long as electronic copies may be used. APHIS should specify that records may be retained as backed-up electronic copies.

Drafted by the SIVB public policy committee, and presented to the board of directors of SIVB for approval.

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