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Genetically engineered crops that fly under the US regulatory radar

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cost reductions over commercially available laboratory and medical equipment, which can exceed 99% (refs. 6,9). Furthermore, aside from computing literacy and initial set-up, no specialist skills are required in the design and manufacture of objects, unless post-production physical or chemical customization is required. Thus, access to these advantages is not restricted by technical ability, but only by a lack of awareness and/or a willingness to embrace such novel technology.

In our hands, we have found 3D printing particularly adept as a catalyst for innovation in the development of preclinical and clinical investigative and/or therapeutic devices. We have used 3D printing across multiple phases of development from prototype to completed product on a variety of devices. These have included flow chambers designed to separate erythrocytes containing malarial trophozoites from those that do not and molds used in the production of an extracorporeal silicone exudate-collecting chamber, as well as a separate customized retainer (**Fig. 1**). This latter combination is currently being employed in conjunction with blister-induced skin windows in a preclinical mechanistic study exploring the effect of systemic inflammation on local immune competence.

In this setting, the benefits of 3D printing are manifest. Progression from concept to draft specification to a testable prototype is rapidly accomplished: basic CAD designs are created and printed in a few hours at 0.2 mm resolution, by one researcher, at a material cost of less than $1/unit. Crucially, this affords rapid iterative design evolution and easy 'scale-up'. Prototypes can be tested, the CAD modified in response to experimental requirements or observations, and revised devices and tools reprinted within a day—a feat impossible using conventional manufacturing techniques.

We thus view the advent of accessible 3D printing as a pivotal moment in translational research for the many, not the few. Not only can scientists and clinicians alike achieve in-house production of routine items with associated cost- and time-saving benefits, but they can also customize existing products or develop entirely new bespoke ones. The free sharing of designs in a participatory, decentralized manner clearly fosters collaboration. Temporally and spatially separated individuals may contribute specialist knowledge to the same design, testing the end product for efficacy and suggesting adaptations. In addition, newly developed translational tools may be rapidly disseminated, accelerating research by other groups while ensuring standardization and reproducibility of results. Individualization of products, particularly relevant to the clinical setting, is also facilitated where modifications to a central or established design are more readily achieved at a pace and cost unachievable by standard manufacturing approaches. Finally, 3D printing may have special applicability in remote or resource-limited environments—often where healthcare and biomedical research are most needed[9,12]. Here, the ability to manufacture laboratory tools and/or clinical equipment from freely available designs using generic materials with low overheads will be of paramount importance, and certainly offers a more viable long-term strategy than the traditional supply (or lack) of expensive, commercially available end products. To paraphrase a proverb "give a researcher a tool and you equip them for a day; teach them how to use a 3D printer and you can equip them for a lifetime."

3D printing has the potential to become as invaluable and common an asset in the medical research laboratory or hospital as the centrifuge or microplate reader. The only factor limiting 3D printing's widespread implementation is a lack of awareness of its accessibility and applications. As bioengineers and clinicians who have integrated 3D printing into our research process, we are excited about the benefits it has already delivered in transforming our timelines and cost structure. We would highly recommend this technology to all those interested in expediting end user–inspired biomedical innovation—get one, you won't regret it.

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Genetically engineered crops that fly under the US regulatory radar

To the Editor:

Recently, the US Department of Agriculture (USDA) Animal and Plant Health Inspection Service (APHIS) has categorized as outside the scope of its regulations several genetically engineered (GE) crops that rely on either new approaches or new wrinkles on traditional recombinant DNA techniques in their provenance. Indeed, a survey of recent inquiries to APHIS suggests that the number of entities seeking nonregulated status for their products has been on the increase. Many of these inquiries originate from public institutions or small biotech companies, suggesting that the use of technologies, such as null segregants, novel delivery systems, cisgenesis/intragenesis and site-directed nucleases, may be a deliberate strategy for smaller entities to navigate the US GE crop regulatory framework. The fact that the US Coordinated Framework is on the one hand failing to oversee these new product types and on the other overregulating GE crops and technologies with proven track records of safety should be a cause for concern. We conclude that it is time to reevaluate the US regulatory framework for GE crops and build a system that is based on science, with enough flexibility to evolve with accumulating scientific knowledge and technologies and, importantly, that allows the participation of small companies and public sector institutions.

Originally established in 1986, the United States' Coordinated Framework for Regulation of Biotechnology[1] sought to ensure that GE crops do not pose a risk to humans, other plants and animals or to the environment. Although the legal basis for this framework has remained largely unchanged since 1986, the technologies and products it aims to regulate have moved substantially beyond their initial reliance on 'pest'-derived transformation systems, which is the primary trigger for regulatory oversight (**Fig. 1**). Today, three decades since the first GE crops were developed, many regard this regulatory framework as obsolete and an obstacle to the development of new agricultural products[2].

Operating under three federal laws, the US Food and Drug Administration, the US Environmental Protection Agency and the USDA are authorized to regulate the food and environmental safety of biotechnological agricultural products (http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/Biotechnology/ucm096126.htm; http://www.epa.gov/pesticides/biopesticides/pips/pip_rule.pdf; http://www.ecfr.gov/cgi-bin/text-idx?SID=108726ba14bc151a29010a681476b349&node=pt7.5.340&rgn=div5). The USDA regulatory process for GE crops is triggered by the use of 'plant pests' in any portion of the modification process or the derived potential of the GE crop to behave as a plant pest (**Box 1**). In practice, the routine use of pest-derived genetic components triggers a *de facto* process-based regulatory regime by the USDA's inspection branch, APHIS.

In recent years, however, products emerging from the technology development pipeline are increasingly falling outside of the scope of APHIS regulations (**Fig. 1**). We present below a review of the body of GE crops that have circumvented APHIS's process-based regulation, which provides insight into how the current regulatory framework works and highlights the incongruity of regulation that is based on process, rather than product.

Developers of GE crops that are uncertain of the regulatory status of new products may seek a determination by APHIS's Biotechnology Regulatory Services (BRS) (http://www.aphis.usda.gov/wps/portal/aphis/ourfocus/biotechnology?1dmy&urile=wcm%3Apath%3A/aphis_content_library/sa_our_focus/sa_biotechnology/sa_regulations/ct_am_i_reg). Over the past two decades, 26 inquiries have been made, and APHIS's determinations are publicly available on the BRS website or through direct solicitation of the information (http://www.aphis.usda.gov/wps/portal/aphis/ourfocus/biotechnology?1dmy&urile=wcm%3apath%3a%2Faphis_content_library%2Fsa_our_focus%2Fsa_biotechnology%2Fsa_regulations%2Fct_reg_loi) (**Fig. 1** and **Table 1**). We sorted the 26 inquiries on the properties of the final plant product, transformation processes or the use of recently developed technologies into several categories (**Table 1**)[3,4]. The major categories are null segregants (Category 1), classic gene delivery systems (Category 2), cisgenics/intragenics (Category 3) and site-directed nucleases (Category 4), with a final group (Category 5) capturing those products that did not fit neatly into the other categories.

Null segregants in Category 1 involve the application of transgenic technologies in the breeding process that are eliminated from the final product. Null segregants are the nontransgenic progeny produced from the selfing or crossing of a transgenic parental line with a nontransgenic elite line. Four of the 26 inquiries fall into this category. Two developers—the USDA's Agricultural Research Service and North Carolina State University (Raleigh)—inquired on the status of progeny derived from a parent engineered for accelerated sexual maturity. The third inquiry was made by researchers at the University of Nebraska (Lincoln) on progeny derived from a transgenic sorghum line modified to epigenetically decrease *MSH1* expression through RNA interference silencing. Because the resulting final products (i.e., the null segregant progenies) do not contain foreign genetic information or genetic material originating from "plant pests" and were produced without the use of plant pests, APHIS determined that these products did not fall within the scope of APHIS regulations and would not be regulated by the USDA.

A similar inquiry was made related to a breeding tool, centromere-mediated chromosome elimination (CCE), a process in which a parental line is engineered such that the heritability of its chromosomes is altered[5]. When the modified line is crossed to wild-type lines, the complete complement of chromosomes (thus the transgene) from the inducer line is eliminated, leaving a haploid plant that, when doubled, results in a pure-breeding line in a single generation. As no plant-pest genetic material is present in the progeny of these lines and no plant pests were used in the production of the final products, APHIS determined that progeny created by CCE would not be considered regulated articles and would not be subject to its regulations.

A second group of nonregulated products relates to gene delivery platforms (Category 2). The classic transformation platform for plant applications exploits the natural transformation capability of *Agrobacterium tumefaciens*, the causal agent of crown gall disease in dicotyledonous plants (and as such a plant pest). In addition, several physical gene transfer techniques have been developed with ballistic bombardment of DNA or biolistics being the most commonly used alternative to *Agrobacterium*-mediated gene transfer for plant transformation.

APHIS has regulated all but two products that used *Agrobacterium*-mediated transformation (AMT). Typically, the use of this known 'plant pest' triggers the process-based regulatory oversight of the USDA, even though the mechanism of pathogenicity is very well understood and disabled in

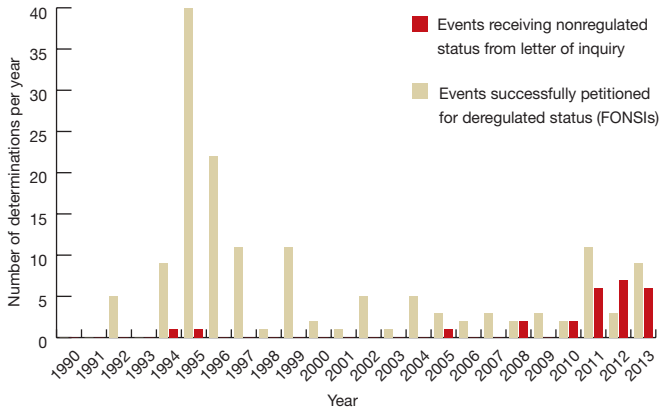

Figure 1 Deregulated and nonregulated status determinations issued by APHIS. Whereas the number of FONSIs (findings of no significant impact; document issued upon successful petition for deregulated status) peaked in the mid-1990s and significantly decreased thereafter, the number of products determined to fall outside of the current regulatory framework has increased only in the past 5 years. Of major interest, 2012 was the first time that the number of nonregulated determinations surpassed the number of FONSIs issued.

Box 1 What is a regulated article?

At the USDA, biotechnology permits are issued under the Code of Federal Regulations, Title 7, part 340 (7CFR Part 340)[16]. These regulations provide the following definitions and scope for a regulated article and plant pest:

Regulated Article. "Any organism which has been altered or produced through genetic engineering, if the donor organism, recipient organism, or vector or vector agent belongs to any genera or taxa designated in §340.2 and meets the definition of a plant pest, or is an unclassified organism and/or an organism whose classification is unknown, or any product which contains such an organism, or any other organism or product altered or produced through genetic engineering which the Administrator determines is a plant pest or has reason to believe is a plant pest. Excluded are recipient microorganisms which are not plant pests and which have resulted from the addition of genetic material from a donor organism where the material is well characterized and contains only noncoding regulatory regions."

Plant Pest. "Any living stage (including active and dormant forms) of insects, mites, nematodes, slugs, snails, protozoa, or other invertebrate animals, bacteria, fungi, other parasitic plants or reproductive parts thereof; viruses; or any organisms similar to or allied with any of the foregoing; or any infection agents or substances, which can directly or indirectly injure or cause disease or damage in or to any plants or parts thereof, or any processed, manufactured, or other products of plants."

the strains used for transformation. Three of the 26 inquiries to BRS cover products developed through AMT. One of these inquiries—a Barrel Medic (*Medicago truncatula*) retrotransposon library developed by the Samuel Roberts Noble Foundation (Ardmore, OK, USA) for research use—resulted in the expected regulated determination. However, the remaining two inquires using AMT—cut carnations with an unlisted trait and developer, and Del Monte's (San Francisco) Rosé pineapple modified for altered ethylene and lycopene biosynthesis—were designated "nonregulated" by APHIS because of the sexually nonviable state at which these products would exist in market. The inquiry responses issued by APHIS highlight the biologically remote potential for (i) outcrossing with wild or commercial varieties, (ii) seed formation and (iii) asexual reproduction and persistence in the environment as the leading basis for its determination in both cases. It is also important to note that these two cases inquired on the import of these products for commerce and not for the environmental release (i.e., large-scale commercial production) of the modified crops.

The basis for 9 of 26 inquiries was to determine the regulatory status of crops engineered using biolistics, rather than *Agrobacterium*, for gene transfer. Examples of these products include the following: petunias genetically modified to produce altered vegetative pigmentation; glyphosate-tolerant Kentucky Bluegrass and St. Augustine grass; high-yielding switchgrass; water-use efficient switchgrass; and several switchgrass lines with altered biomass composition for use as biofuels. For all of these cases, the products were determined to be nonregulated articles as neither the genetic donor/recipient organism nor the vector/vector agent used to mediate the genetic transformation were derived from known plant pests.

Category 3 crops that fall outside regulated status include those produced by cisgenesis and intragenesis. Cisgenesis and intragenesis are terms used to describe plants that are genetically modified using genes and genetic elements exclusively from a sexually compatible donor. Cisgenesis uses only genetic elements from the same species, whereas intragenesis exploits genes and regulatory elements from a member of a cross-compatible species. It has been suggested that cisgenic or intragenic plants should not be regulated as transgenic but perhaps by a separate, but as yet undefined, regulatory framework[6,7].

In the same category, two inquiries were made on products that sourced donor genetic material from species sexually compatible with the recipient: scab-resistant apples developed at Wageningen University (Wageningen, the Netherlands) and grapes with elevated anthocyanin biosynthesis developed by the University of Florida (Gainesville). Interestingly, APHIS determined that the cisgenic scab-resistant apple variety should be regulated because it was developed by AMT. In contrast, the intragenic grapes with altered anthocyanin content received nonregulated determination from APHIS because they were modified with grape gene sequences delivered by biolistics (i.e., no plant pests were used in the transformation process). In essence, APHIS disagreed with assertions that the use of genes from sexually compatible species is inherently different from the use of transgenes for crop improvement, and APHIS has not treated cisgenics or intragenics differently from other transgenic crops.

In category 4, site-directed nucleases represent the latest development of precision or new breeding techniques used for improving agricultural products. These nucleases take advantage of the DNA repair and replication enzymes found in nature to cleave double-stranded DNA and activate the cell's DNA repair machinery. This diverse group of breeding tools includes zinc-finger nucleases (ZFNs), meganucleases, transcription activator-like effector nucleases (TALENs) and the clustered, regularly interspaced, short palindromic repeats (CRISPR), which together with CRISPR-associated proteins (Cas), constitute the CRISPR-Cas system. In each case, the nuclease allows the introduction of a wide range of changes into the host genome, including nucleotide-specific changes and/or deletions or large (whole gene) insertions or substitutions, similar to changes derived by naturally occurring transposons typical in plants[8].

Two inquiries were made on techniques that precisely modify specific nucleotide sequences within the genome: maize with reduced phytate, developed using ZFNs, and genomic modifications mediated by meganuclease I Cre1. APHIS determined that both of these technologies have the potential to create two classes of products: (i) those in which endogenous genetic material is removed (targeted deletions); and (ii) those in which precise sequence changes are introduced by using specific template oligonucleotides (targeted substitutions and insertions). APHIS, in both cases, stated that products resulting from targeted deletions would, in most cases, not be regulated because no new genetic material is integrated into the recipient genome, and the engineered nucleases did not originate from plant pests. The second class of products (targeted substitutions and insertions) would need to be reviewed on a case-by-case basis to assess the inserted trait and determine regulatory status.

Table 1 Letters of inquiry to APHIS on regulated status

Category	Inquiry date	Applicant	Host organism	Genetic modification/ phenotype	Transformation method	Status
Category 1; null segregants	1/18/11	USDA Agricultural Research Service	Plum	Accelerated breeding	None listed	–
	1/22/11	North Carolina State University	Tobacco	Accelerated breeding	None listed	–
	12/10/11	University of Nebraska	Sorghum	Decreased MSH1 expression	*Agrobacterium tumefaciens*	–
	1/27/11	New Zealand Institute for Plant and Food Research	N/A	CCE/production of double haploids	None listed	–
Category 2; gene delivery systems	3/8/95	None listed	Carnation	None listed	*Agrobacterium tumefaciens*	–
	9/1/09	Samuel Roberts Noble Foundation	Barrel Medic (*Medicago truncatula*)	*Tnt1* retrotransposon expression (knockout library)	***Agrobacterium tumefaciens***	Regulated
	7/30/12	Del Monte Fresh Produce Company	Pineapple	Altered fruit tissue color and anthocyanin content	*Agrobacterium tumefaciens*	–
	12/11/07	New Zealand Crop and Food Limited	Petunia	Altered vegetative pigmentation	Biolistics	–
	9/13/10	Scotts	Kentucky Bluegrass	Glyphosate tolerant	Biolistics	–
	1/20/12	Ceres	Switchgrass	Improved biofuel yield potential	Biolistics	–
	1/31/12	Scotts	Kentucky Bluegrass	Glyphosate tolerant, enhanced turfgrass quality	Biolistics	–
	2/1/12	Scotts	St. Augustine grass	Glyphosate tolerant, enhanced turfgrass quality	Biolistics	–
	7/23/12	Ceres	Switchgrass	Enhanced water-use efficiency	Biolistics	–
	7/23/12	Ceres	Switchgrass	Biomass more easily converted to fermentable sugars	Biolistics	–
	7/23/12	Ceres	Switchgrass	Biomass more easily converted to fermentable sugars	Biolistics	–
	7/23/12	Ceres	Switchgrass	Biomass more easily converted to fermentable sugars	Biolistics	–
Category 3; cis-/intra-genesis	2/23/12	Wageningen University	Apple	Scab (disease) resistant (cisgenic)	***Agrobacterium tumefaciens***	Regulated
	2/8/12	University of Florida	Grape	Increased anthocyanin production (intragenic)	Biolistics	–
Category 4; SDNs	3/1/10	Dow	Corn	Suppressed phytate biosynthesis	Zinc-finger nuclease (EXZACT) deletions	–
					Zinc-finger nuclease (EXZACT) substitutions or additions	Regulated[a]
	9/9/11	Cellectis	N/A	Genome editing (targeted indels)	Meganuclease (I-Cre1) deletions	–
					Meganuclease (I-Cre1) substitutions or additions	Regulated[a]
Category 5; other	3/7/94	Washington State University	*Rhizobium leguminosarum*	Insect tolerance	None listed	–
	2/16/05	V.P. Technology Development	*Chlamydomonas reinhardtii* HSV8	Expression of antibodies for human therapeutics	None listed	–
	4/6/08	Coastal Biomarine	Algae strains	Expression of glucose transporter from *Chlorella*	None listed	–
	2/21/11	Danziger	Baby's Breath	Altered flower color	None listed	–
	6/15/12	BioGlow	CBI	CBI	CBI	–
	10/23/12	BioGlow	CBI	CBI	CBI	–

Listing of all the publicly available letters of inquiry made on a product's regulatory status. Boldface text indicates the understood reason for a 'regulated' status determination. CBI, confidential business information; SDN, site-directed nucleases; CCE, centromere-mediated chromosome elimination; N/A, not available used where information *cannot* be provided in a given column, such as when an inquiry was on a specific transformation process as opposed to a specific product (e.g., CCE, a process/tool, with no specific host organism); None listed, used where information *can* be provided but none was found or listed in the primary (publicly available) sources; —, used when inquired product/process was determined to "fall outside of 7CFR Part 340 scope". The authors felt it inappropriate and/or potentially misleading to assign a "non-regulated" status (as different statuses may exist in other regulating agencies).

[a]GE crops modified by targeted deletions, during which no 'plant pest' genetic information is incorporated into the host genome, were determined to fall outside of the scope of 37 CFR Part 340 (ref. 16; **Box 1**); GE crops modified by targeted insertions would have to be reviewed on a case-by-case basis to determine regulatory status.

We were unable to classify the remaining 6 (of a total 26) inquiries in our analysis as limited information was provided on the transformation processes in the original inquiries or in APHIS's subsequent response (**Table 1**; Category 5). Two of these inquiries pertain to modified algae strains: a cocktail of three marine algae (*Nannochloropsis occulata*, *Isochrysis tahitia* (*T-iso*) and *Chaetocerous mulleri*) engineered with a glucose transporter from *Chlorella* for biofuel production; and a *Chlamydomonas reinhardtii* strain developed for production of antibodies in human therapeutics. Both inquiries were determined by APHIS to not meet the criteria necessary to trigger regulation.

Another inquiry sought a determination on four strains of *Rhizobium leguminosarum* bv. *vicieae* engineered to express the insecticidal *cryIII* gene from *Bacillus thuringiensis* subsp. *tenebrionis* for use in a planned, small-scale field experiment. Though the taxonomic family to which these strains belong is listed among the known plant pests, APHIS determined that these products would not be regulated stating that "the specific recipient [*R. leguminosarum* bv. *vicieae*] which is to be employed [by the] genetically engineered construct is not a 'plant pest' by definition" as the primary reason for the nonregulated determination.

The remaining three inquiries relate to ornamental products. One of these inquired on the status of imported cut Baby's Breath, modified with altered flower color. Although no information was provided on the transformation process used, APHIS determined these cut flowers to be nonregulated products citing, again, the remote potential for (i) outcrossing with wild varieties, (ii) asexual reproduction, and (iii) seed formation and dissemination. The last two inquiries originate from BioGlow (St. Louis, MO), a small biotech company developing autoluminescent plants. Although most of the publicly available inquiries are heavily redacted confidential business information, APHIS determined these products do not meet the criteria necessary to trigger regulation stating the absence of plant pests as their primary reason.

To summarize, our survey reveals that a large number of inquiries at the USDA are now considered to fall outside oversight. Interestingly, inquiries seeking nonregulated status of GE crops are increasing, and it is striking how many come from public sector institutions or small to medium-sized enterprises, rather than the typical multinational seed-agrochemical companies that have traditionally developed GE crops. It is possible that adopting approaches to seed production that avoid the costly US Coordinated Framework for GE crops may be a deliberate strategy for smaller entities.

The US regulatory framework for GE crops has been a topic of discussion for nearly 30 years. The framework has the advantage that it is transparent and gives producers of GE crops clear guidance to achieve regulatory approval; however, it has also been criticized for being overly burdensome and not based on evolving science or on the >25 years of experience in assessing the impact of GE crops on humans, animals and the environment. Although several countries have initiated the necessary discussion to address emerging agricultural products and technologies, the United States remains the only country with a case history of challenges and determinations on the regulatory status of crops modified using modern technologies and genetic elements.

As long as the regulatory framework exists in its current form, it seems likely that seed developers, especially those without deep pockets, will continue to adopt technologies that allow them to sidestep US regulatory oversight to achieve commercial deployment of GE crops. Although this result may, on balance, be positive in terms of unleashing the innovative potential of small companies and public sector universities and organizations—the multinational corporations that have dominated the field for the past decade and a half do not have a glowing record in terms of innovation beyond traits for pesticide and herbicide resistance—it is an outcome that relies on a 'loophole' created by a regulatory system that is process, rather than product, based.

It is unlikely that supporters or detractors of GE crops can be satisfied with a system that on the one hand over-regulates crops and technologies that have proven track records of safety and on the other hand fails to provide oversight of crops that are reasonably considered to be GE. A sufficiently large body of scientific literature on the GE traits developed so far indicates that the early health, safety and environmental concerns[9,10] have not materialized, thus DNA modification *per se* is not inherently unsafe or a threat to the environment[11–15].

In our opinion, a rational, science-based regulatory system should not regulate products based on null segregants (Category 1) because they contain no genetic modifications. Similarly, products generated by site-directed nucleases should not be regulated because they use the natural DNA repair and replication enzymes found in living organisms and result in changes that could be a result of conventional breeding.

It is time to critically reconsider the regulatory framework for GE crops and build a system of oversight that is product- and science-based. This system should have enough flexibility to evolve with accumulating scientific knowledge and new technologies, and, importantly, allow the participation of small companies and public sector institutions to fulfill the range of innovation needed to sustainably meet the next decades' agricultural needs.

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The authors declare no competing financial interests.

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