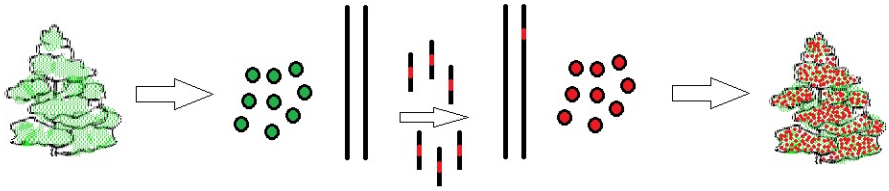

Figure 1 The ODM technique can be applied to plants grown *in vitro*. Specific oligonucleotides (short black lines), typically 20–100 base pairs in length, are transferred to cells or protoplasts isolated from the original plant. The oligonucleotides are homologous to the DNA of the original plant (long black double line), with exception of a single-base-pair change (red spot in short black line). During cell division, the short oligonucleotide sequence binds to the corresponding homologous plant DNA sequence. The repair mechanism of the plant cell recognizes the single-base-pair change and repairs its own DNA accordingly. Cells carrying the point mutation can then be regenerated to full plants through conventional tissue-culture methods.

grafting on transgenic rootstock, cisgenesis/intragenesis and reverse breeding. As early as October 2007, the EC set up a working group to assess whether several new breeding technologies could or would fall within the scope of the GMO legislation[9]. In 2011, the New Techniques working group published an 'unofficial' final report (which is not available on the EC website[9], but is available as ref. 10). The report claims that "the views expressed… are those of an expert working group and do not necessarily represent those of the [EC] or the Competent Authorities. Only the European Court of Justice can give a binding opinion on EU law." The technologies selected for that report and the resulting products were assessed in accordance with the existing EU legislation on GMOs. The expert evaluations clearly indicate that many techniques such as ODM, DNA endonucleases and reverse breeding develop organisms that cannot be distinguished at the molecular level from those developed through 'conventional' breeding techniques or through selection in natural populations. Thus, the report concludes, new breeding technologies can be considered "as a technique of genetic modification yielding organisms to be excluded from the Directives"[10]. Others have pointed out that existing directives 2001/18/EC and 2009/41/EU, and regulations (EU) 428/2009 offer sufficient guidance to ensure biosafety and biosecurity of plants generated by use of new breeding technologies[11]. However, as yet, no final decision has been made by the EC with regard to their regulatory assessment.

Once again, European authorities dally, caught between satisfying science, the seed industry, the organic lobby and anti-GM zealots, leaving plant breeders uncertain how to use cutting-edge technology in the old world. Meanwhile, Cibus canola is cultivated in the United States, and products are sold at a premium (in the EU and elsewhere), as non-genetically modified products.

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1. Cibus website, accessed 9 September, 2015 http://www.cibus.com/
2. Wagner, D. *Genetic Literacy Project* 7 July, 2015 http://www.geneticliteracyproject.org/2015/07/07/gmo-or-not-is-a-new-genetically-edited-herbicide-tolerant-canola-oil-a-gmo/.
3. Seldon, S. *Cibus Press Release* accessed 9 September, 2015 http://www.cibus.com/press/press012709.php
4. Kommission für die Biologische Sicherheit (ZKBS). Position statement of the ZKBS on new plant breeding techniques (June 2012) http://www.bvl.bund.de/SharedDocs/Downloads/06_Gentechnik/ZKBS/02_Allgemeine_Stellungnahmen_englisch/05_plants/zkbs_plants_new_plant_breeding_techniques.pdf;jsessionid=8F399F519D186BB422E195AC16EBF06F.2_cid350?__blob=publicationFile&v=2
5. Federal Office of Consumer Protection and Food Safety (BVL). Letter of response regarding Cibus' inquiry that ODM-canola is not a GMO according to the German GenTG. (5 February, 2015) http://www.umweltinstitut.org/fileadmin/Mediapool/Bilder/01_Themen/04_Gentechnik/Neue_Gentech-Methoden/BVL_Cibus.pdf
6. Bahnsen, U. Finden Sie den Unterschied! (*Find the difference!*) *Zeit Online* (16 April, 2015) http://www.zeit.de/2015/16/gentechnik-raps-neue-sorte-anbau-deutschland
7. Federal Office of Consumer Protection and Food Safety (BVL) (3 June, 2015) Widerspruch gegen CIBUS Raps-Bescheid zurückgewiesen *(Rejected opposition to CIBUS canola decision)*. (3 June 2015) http://www.bvl.bund.de/DE/06_Gentechnik/04_Fachmeldungen/2015/2015_06_03_Fa_CIBUS.html
8. Informationsdienst Gentechnik, Cibus-Raps darf vorerst nicht aufs Feld *(Cibus-canola not allowed to grow on the field)* (30 July, 2015) http://www.keine-gentechnik.de/nachricht/30970/.
9. European Commission. New plant breeding techniques (accessed 11 January, 2016) http://ec.europa.eu/food/plant/gmo/new/legislation/plant_breeding/index_en.htm
10. European Commission. *New Techniques Working Group. Final Report* (EC; Brussels, 28 October, 2011) http://www.keine-gentechnik.de/fileadmin/files/Infodienst/Dokumente/2011_Report_of_the_Working_Group_on_New_Techniques_Final.pdf Accessed 11 January 2016.
11. Buhk, H.J. *N. Biotechnol.* **31**, 528–531 (2014).

Ending event-based regulation of GMO crops

To the Editor:

Getting regulation of agricultural biotechnologies right is no simple task. Stringent regulations for genetically modified organisms (GMOs) in the European Union (EU: Brussels) have nearly stifled the use of biotech crops on farms or in derived foods there, and in the United States the diversified 'Coordinated Framework' has produced a strange patchwork of rules, exceptions and lengthy delays. As the Editorial in the December issue highlights[1], the US Executive Branch has launched a process to reform its regulatory structure, calling for an integrated system that recognizes and balances safety, environment, innovation and economic growth[2]. On the heels of the release of a White House memo, the US House of Representatives passed the Safe and Accurate Food Labeling Act of 2015, which is on its way to the Senate for consideration. Contrary to current regulations, this legislation would explicitly preempt state-by-state labeling and require the US Food and Drug Administration (FDA) to conduct a safety review for all GMOs entering commerce[3]. This recent activity by both the executive and legislative branches provides a welcome opportunity to take a fresh look at

the entire GMO regulatory system, including its very foundations. We argue here that revisions are badly needed to better align the GMO regulatory system with the substantial body of science and experience that has accumulated since the 1986 Coordinated Framework was established, almost three decades ago.

A key issue is the very high cost imposed on all types of GMOs by our national and international regulatory systems[4]. This is a major factor preventing most small companies and public sector breeders from using GMO methods[5]. The White House memo cited that "…costs and burdens [of the current regulatory system] 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…". This recognizes that the current regulations have the practical consequence of keeping innovations out of the marketplace, including more environmentally friendly or healthy alternatives.

One of the main reasons for the high costs of GMO regulations is the need to obtain approvals, and track or in some cases label, individual gene-insertion events. This is true not only in the United States, but also for international trade given Codex Alimentarius' food safety assessment framework for recombinant DNA technology[6]. The US Environmental Protection Agency (EPA), for example, treats each event as a unique biological entity, called a Plant-Incorporated Protectant (PIP), triggering a review under 40 Code of Federal Regulations Parts 152 and 174. This entails a new regulatory review, even if the genetic construct is known to produce an identical biochemical as a previously approved PIP[7,8].

In research, it is important to keep track of events as the effects and expression of independently inserted genes vary widely (e.g., ref. 9). For commercial use, however, one or a few events with stable and effective levels of gene expression, and an absence of major pleiotropic effects, are selected early in development[5]. Position effects owing to gene insertion are also likely to become much reduced over time as site-directed insertion using clustered, regularly interspaced, short palindromic repeats (CRISPRs) or similar tools becomes more commonplace. The high variance seen in research, and in earlier forms of undirected gene insertion, will have increasingly little relevance to commercial events and their regulation.

Moreover, approving a single event does not mean that a well-defined, homogeneous type of genetic change has been imparted. Once transgenic events are moved into a wide variety of genetic backgrounds during breeding, or are used under the great variation in environment and management practices common in agriculture, they will show enormous variation in gene and associated trait expression[10].

For clonally propagated and highly heterozygous crops, such as tuber crops and many types of perennial fruit and fiber-producing shrub or tree crops, the goal is to insert or modify genes while keeping the overall genotype—which has been highly selected and often well known to growers and consumers—intact. Recent examples of such crops are the deregulated Arctic Apple and Innate Potato. For these types of crops, the goal is to commercialize many insertion events (one or several per variety)[11]. Although the US Department of Agriculture has an 'extension' system in place to facilitate deregulation of such additional events, it has been rarely used (19 times of 123 deregulations[11,12]). Newly issued guidance on this system[13] appears to be forward looking, in stating that it will consider similarity in "mechanism-of-action," including results from similar traits in other species as well as from the same genes in other events of the same species, but it also suggests providing essentially the same data as for new deregulatory packages, thus might in practice be little different in costs and delays from the current system.

The current regulatory milieu takes little or no explicit consideration of new methods, including genome editing and RNA interference (RNAi), that modify the structure and expression of native genes much as breeding does, but with greater precision[14]. With the exception of Canada (which regulates based on trait novelty not method), the process of conventional plant breeding is, in practice, essentially exempt from explicit regulation in the United States and all other countries, and there is little interest in imposing strong 'GMO-esque' types of regulations on it. Thus, based on science, GMO methods that create novelties and unpredicted variations similar to those of conventional plant breeding should receive a similar level of method-based regulation—which in most cases is none.

A major cost of the international event-based system is the millions to billions of dollars of lost value due to cancelled, returned or degraded value of shipments—including that from legal settlements—as a result of the admixture of approved and unapproved events in commerce (e.g., refs. 15,16). Because several events are often tested in the field during advanced research and early breeding, low levels of adventitious presence due to imperfectly controlled pollen and seed dispersal, or human error, are likely. The risk is especially high for wind-pollinated crops, trees and grasses[17], and presents a huge economic risk to companies and societies that has little biological merit.

A key early rationale for event-specific regulation was food safety. As originally constructed, the FDA's guidance report centered on concerns over unintended effects resulting from the gene insertion process. This concern motivated FDA to issue a guidance report stating its concern that genetic engineering technology could induce the expression of natural toxicants[18]. In its 1992 guidance report, the FDA also acknowledged that "scientific advancements in this field are occurring rapidly, [and the] FDA will refine its policy, if circumstances warrant, in a future Federal Registrar notice." Furthermore, the FDA stated: "based on experience, the likelihood of a safety hazard is typically very low."

Since the FDA stated its concerns over unintended effects of GMOs in 1992, there have been many dozens of studies of unintended effects of gene insertion, and numerous studies have compared the 'omic' variation—a rough indicator of the relative extent of unintended changes in physiology owing to the gene insertion process—among the products of conventional plant breeding to those of normal, healthy plants (similar to those which might be used commercially) resulting from different gene insertions. Such analyses have failed to find any cases where there was elevated production of a worrisome toxin[19,20] or where omic variation exceeded that resulting from conventional breeding; in fact, generally there was far less variation in the GMOs than in conventionally bred crops[21]. Moreover, in most cases, agriculturally routine environmental variation exceeded variation from both GMO and conventional genetic modification[21,22]. In some cases omic changes are seen and intended, such as when a gene modifies overall physiology (e.g., anthocyanin overproduction in tomatoes[23]), but these are intended and should be the subject of scrutiny to confirm they are beneficial as intended, comparable to similar results from conventional breeding, or at least not deleterious.

In recent years, as knowledge of genomes has increased, it has become clear that

DNA undergoes extensive and dynamic changes in nature and under conventional breeding. These studies show evidence of far greater structural, epigenetic and gene-expression variation than had been expected, in general, far exceeding those imparted by genetic engineering (e.g., refs. 11,24,25,26). Moreover, the variations observed are of little consequence for food safety. Weber *et al.*[24] concluded that "…neither changes in gene expression nor mutations in amino acid sequences are likely to alter the safety of a protein or lead to the production of novel metabolites. Thus far, there is no evidence that a random genomic change in a crop has ever resulted in a novel safety issue, even when new alleles or genes were created." Extensive transposition, where genes and promoters are moved throughout genomes, and normal mutational processes and DNA repair, provide a continual source of potential novelty in the kinds and degrees of modification of gene expression throughout the genome. Gene gains, losses and duplications are also common. Gene insertion appears to be a small impact by comparison to the ongoing dynamic variation in gene and genome structure during evolution and breeding[22,24]. Thus, the risk of unintended expression of endogenous toxic proteins from genetic engineering is no greater than conventional breeding, and in most cases far less.

So what should the new US Coordinated Framework, and ultimately a global coordinated framework, look like?

First, it should be novelty- and risk-based, not method-based or a strange hybrid, which the current Framework has evolved to be[27,28]. A recent public call for comments by the USDA included a proposal to consider risk as a threshold factor for regulation[29]. If a novel protein, novel change to food composition or novel change to the environment is imparted, it—and it alone—should be the focus of regulatory analysis. And this analysis should be forward-looking rather than backward-looking; the environment is changing rapidly, and we cannot regulate as though environments will be static or can be restored to former conditions[30], a consideration that is especially germane to trees and other perennials with long generation times[27].

Second, the Framework should shift away from event-based analysis to product-based analysis. In this circumstance, classes of transgene constructs, species and environments should be the focus, with developers making as broad a case as can be scientifically justified from data and theory. Initially, research would logically focus on compositional and environmental analysis of multiple events to support generalizations, but subsequent events with the same or similar constructs would be exempt from the need for event-based data. In many cases, and increasing over time, compositional analysis could be excluded entirely based on prior experience and biological knowledge of the changes imparted[31]. Similar ideas are under consideration in the United Kingdom[32], and a framework has been proposed in Argentina to reduce the delays from repetitive event-based decisions[33].

Third, because of the severe commercial risks of adventitious presence (AP), workable tolerances should be established early in research and breeding that has national and international recognition. This should not be scientifically difficult to justify with new versions of already commercially approved genetic modifications, but a process should also be put in place to do the same for new genes where there is scientific reason to believe that AP does not pose a greater threat to food or environmental safety than similar AP from conventional breeding (which often uses exotic germplasm with considerable toxicity and environmental spread concerns). The FDA addressed this concern in a guidance report issued in 2006, which suggested an early consultation process for food safety evaluation because of risk of AP in in field tests[34]. The revised Coordinated Framework should consider providing an opportunity for the use of an affirmative defense (or similar legal strategy) to limit legal liability associated with AP when scientifically justified. Notwithstanding the obvious political challenges to making such changes given the highly restrictive, event-based policies of other nations, the United States and its partners (e.g., Organisation for Economic Cooperation and Development (OECD) countries) should lead in developing a new, coordinated international regulatory framework.

Fourth, it is essential that the roles of the agencies are clearly defined; according to the White House memo[2], the administration intends to clarify "…the current roles and responsibilities of the EPA, USDA, and FDA in the regulatory process. This update will help clarify which biotechnology product areas are within the authority and responsibility of each agency and outline how the agencies work together to regulate products that may fall under the authorities of multiple agencies."[2] It is our hope that the process will result be much better 'discipline' of what appears to be striking overreach by the EPA, which effectively defines the mobilization of highly specific natural plant defense systems against pathogens by RNAi as 'pesticides', and also appears willing to assert authority to regulate all growth-modified GMO crops under the same authority[35]. In practice, this PIP designation also means that the plant is treated as a pesticide-producing entity—meaning substantial pre-market and post-market regulatory requirements similar to what would apply to a pesticide-manufacturing facility. This can have perverse unintended consequences. For example, virus-resistant Honey Sweet plum, which was deregulated by USDA and considered safe by the FDA, was flagged by EPA as a PIP, even though the plum does not produce any new pesticides; rather, it is resistant to the plum pox virus as a result of the induction of natural RNAi pathways[7,8,36].

Fifth, modifications that are analogous to what occurs in conventional breeding, but are more precise and better understood (i.e., highly specific directed mutations, nucleotide sequence changes and modifications in expression through gene editing or RNAi), should be exempt unless a novel product-based risk is identified. This proposal does not suggest that all of the products of recombinant DNA methods will be unregulated, but that the method itself will no longer be an automatic trigger for stringent regulation. For example, products whose properties materially affect food safety or the use of registered pesticides will continue to be regulated by FDA and EPA, respectively. Correspondingly, in the rare cases where the fine details of expression of an insertion event matter to risk, such as when a complete absence of a biopharma or pest-resistance molecule in a specific plant organ is important to risk mitigation, event-specific analyses could be specifically required.

Sixth, reasonable timelines for regulatory review should be created and enforced. The costs associated with a review are not only driven by the requirements, but by the timeframe. On average, it takes 13 years and $136 million to bring a GMO product to market, meaning that it is predominantly only major companies with a crop of broad and large-scale appeal that can afford the regulatory hurdles[4].

Finally, a national registry of event-by-event modifications that are put into commerce should be created. Because it is very unlikely there will be national or global agreement on regulatory safety or acceptability of classes of GMOs any time soon, we suggest a requirement to register the changes made even for exempted modifications so they can, where feasible, be detected, and a system can be set up to enable tracking of the changes by those who wish to do so. Such a system, termed the Biosafety Clearing House, is already in place under the Convention

on Biological Diversity (CBD 2015). This is essential for managing the trade and market risks of current 'loophole' biotech products that do not use plant pest vectors or sequences[37].

GMO methods are powerful tools. Contrary to the few dominant types of products in use today, there is an extraordinarily rich pipeline of beneficial products[38], and many more that have been demonstrated in scientific literature. A highly precautionary approach as that embodied in the current Coordinated Framework may have been a reasonable approach to reduce risk and assuage public fears when GMO methods were first entering the marketplace, but it seems that intensive regulation that goes far beyond the requirements of science has often had the opposite effect on public confidence[39]. Although event-specific regulation is only one part of the high cost of regulatory compliance, its removal, together with other regulatory and market adjustments, should help to democratize genetic engineering technology so it can be used to deliver a much greater diversity of innovations to the marketplace.

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1. Anonymous. *Nat. Biotechnol.* **33**, 1213 (2015).
2. Holdren, J., Shelanski, H., Vetter, D. & Goldfuss, C. Memoradum for heads of Food and Drug Administration, Environmental Protection Agency, and Department of Agriculture: modernizing the regulatory system for biotechnology products. White House (2015) (accessed April 16, 2016) https://www.whitehouse.gov/sites/default/files/microsites/ostp/modernizing_the_reg_system_for_biotech_products_memo_final.pdf
3. Pompeo, M. Protecting our farmers, feeding the world. (2015) (accessed April 16, 2016) http://pompeo.house.gov/uploadedfiles/safla_fact_sheet_-_114th_congress.pdf
4. Prado, J.R. *et al. Annu. Rev. Plant Biol.* **65**, 769–790 (2014).
5. Miller, J.K. & Bradford, K.J. *Nat. Biotechnol.* **28**, 1012–1014 (2010).
6. World Health Organization and Food and Agricultural Organization of the United Nations. Codex Alimentarius: Foods Derived from Modern Biotechnology, 2nd edn. (2009) (accessed April 16, 2016) ftp://ftp.fao.org/docrep/fao/011/a1554e/a1554e00.pdf
7. US Environmental Protection Agency Office of Pesticide Programs. EPA's Regulation of Biotechnology for Use in Pest Management (2014) (accessed April 16, 2016) https://www.epa.gov/regulation-biotechnology-under-tsca-and-fifra/epas-regulation-biotechnology-use-pest-management
8. US Environmental Protection Agency Office of Pesticide Programs. Current & Previously Registered Section 3 PIP Registrations (2011) (Accessed April 20, 2016) https://www3.epa.gov/pesticides/biopesticides/pips/pip_list.htm (Accessed April 20, 2016)
9. Cocciolone, S.M., Sidorenko, L.V., Chopra, S., Dixon, P.M. & Peterson, T. *Genetics* **156**, 839–846 (2000).
10. Adamczyk Jr., J.J. Jr & Meredith Jr., W.R. *J. Cotton Sci.* **8**, 17–23 (2004)
11. Adamczyk Jr., J.J. Jr & Meredith Jr., W.R. J. Cotton Sci. 8, 17-23 (2004) Bradford, K.J., Van Deynze, A., Gutterson, N., Parrott, W. & Strauss, S.H. *Nat. Biotechnol.* **23**, 439–444 (2005).
12. USDA - APHIS - Biotechnology. Petitions for determination of nonregulated status. (Accessed April 20, 2016) https://www.aphis.usda.gov/biotechnology/petitions_table_pending.shtml
13. USDA-APHIS Biotechnology. Request to Extend Nonregulated Status from a Previous Determination: Extension Guidance for Developers (2016) (Accessed April 20, 2016) https://www.aphis.usda.gov/brs/aphis-docs/guidance_ext_nonreg.pdf
14. EASAC Statement on New Breeding Techniques. (Euoropean Academies Science Advisory Council, 2015) (Accessed April 20, 2016) http://www.epsoweb.org/file/2105
15. Thukral, N. & Maeda, R. *Reuters* (30 May 2013) (Accessed April 20, 2016) http://www.reuters.com/article/2013/05/30/us-wheat-asia-idUSL3N0EB1JC20130530
16. NBC News (19 March 2015) (Accessed April 20, 2016) http://www.nbcnews.com/news/us-news/monsanto-pay-350k-settle-more-wheat-related-lawsuits-n326811
17. Strauss, S.H. *et al. Bioscience* **60**, 729–741 (2010).
18. US Food and Drug Administration. Statement of Policy—Foods Derived from New Plant Varieties: Guidance to Industry for Foods Derived from New Plant Varieties. *FDA Federal Register* **57** (1992) http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/Biotechnology/ucm096095.htm
19. Herman, R.A. & Price, W.D. *J. Agric. Food Chem.* **61**, 11695–11701 (2013).
20. Steiner, H.-Y. *et al. Plant Physiol.* **161**, 1587–1594 (2013).
21. Ricroch, A.E. *N. Biotechnol.* **30**, 349–354 (2013).
22. Schnell, J. *et al. Transgenic Res.* **24**, 1–17 (2015).
23. Povero, G., Gonzali, S., Bassolino, L., Mazzucato, A. & Perata, P. *J. Plant Physiol.* **168**, 270–279 (2011).
24. Weber, N. *et al. Plant Physiol.* **160**, 1842–1853 (2012).
25. Schmitz, R.J. *et al. Nature* **495**, 193–198 (2013).
26. Shi, J. & Lai, J. *Curr. Opin. Plant Biol.* **65**, 47-53 (2015).
27. Strauss, S.H., Costanza, A. & Séguin, A. *Science* **349**, 794–795 (2015).
28. Giddings, L.V. & Chassy, B. Igniting agricultural innovation: biotechnology policy prescriptions for a new administration. *Science Progress* (2009) (Accessed April 20, 2016) http://scienceprogress.org/2009/07/igniting-agricultural-innovation/
29. USDA APHIS, Environmental Impact Statement; Introduction of the Products of Biotechnology. Fed. Reg. **81**: 6225-6229 (2015).
30. Williams, J.W. & Jackson, S.T. *Front. Ecol. Environ* **5**, 475–482 (2007).
31. Herman, R.A., Chassy, B.M. & Parrott, W. *Trends Biotechnol.* **27**, 555–557 (2009).
32. UK Parliament. *News from Parliament* (2015) (Accessed April 20, 2016) http://www.parliament.uk/business/committees/committees-a-z/commons-select/science-and-technology-committee/news/report-gm-precautionary-principle/
33. Beker, M.P. *et al.* Development of Construct Based Risk Assessment Criteria for GE crops. in *ILSI Argentina Biotechnology Committee Task Force* (2014).
34. US Food and Drug Administration. Biotechnology, guidance for industry: recommendations for the early food safety evaluation of new non-pesticidal proteins produced by new plant varieties intended for food use (2006) http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/Biotechnology/ucm096156.htm
35. Kershen, D. & Parrott, W. *NABC Report* **26**, 159–168 (2014).
36. Sparks, B. *Growing Produce* (2010) (Accessed April 20, 2016) http://www.growingproduce.com/uncategorized/epa-labels-honeysweet-plum-as-a-pesticide/
37. Camacho, A., Van Deynze, A., Chi-Ham, C. & Bennett, A.B. *Nat. Biotechnol.* **32**, 1087–1091 (2014).
38. Ricroch, A.E. & Henard-Damave, M.C. *Crit. Rev. Biotechnol.* **26**, 1–16 (2015).
39. Wiedemann, P.M. & Schütz, H. *Environ. Health Perspect.* **113**, 402–405 (2005).

Regulate genome-edited products, not genome editing itself

To the Editor:

The plants and animals that we raise for food are vastly higher yielding today than they were in decades and centuries past, and they are often more nutritious. These improvements result largely from selective breeding programs that began with domestication in prehistoric times and that continue today with the help of sophisticated statistical analyses informed by extensive data on genomic and phenotypic variation within and between strains or breeds. This endeavor has long been, and continues to be, remarkably successful at achieving its main aims.

However, selective breeding has drawbacks. It is slow; identifying desirable new genetic variation is a matter of chance; selection for specific traits may inadvertently leave behind favorable variants that existed in the parental strains; and deleterious mutations may be propagated unintentionally through linkage with advantageous variants. Recently developed methods for targeted genome editing offer a way to resolve these difficulties, which arise inevitably in conventional breeding programs. Genome editing can be used to make genetic alterations identical to naturally occurring variants. Here, we argue that such alterations logically fall outside of current federal regulatory purview. We develop the general argument by way of a specific proposed application to livestock described on p. 479 of this issue[1]—genetic dehorning of cattle. We conclude by calling for regulators to focus oversight on genome-edited products rather than the process of genome-editing itself.

Dehorning of cattle is a good example of a labor-intensive procedure that could benefit from genome editing. The wild ancestors of