US regulators grapple with oversight of New Breeding Techniques (NBTs)

In the first installment of this series, we looked at the regulatory framework in the US for the products of breeding via recombinant DNA, with an emphasis on crops. In this installment we are looking at the regulation of the products of gene editing and other new breeding techniques (NBTs). In the next installment we look at animal breeding.

What are NBTs?

For an explanation, the GLP's GMO FAQ addresses the subject:

> New breeding techniques (NBTs) are new methods of genetic engineering that give scientists the ability to more precisely genetically modify crops and animals. Using NBTs, researchers can enhance or silence or insert or remove desired traits. Scientists usually move genes from within species (although there are a few transgenic examples of NBTs), bypassing a common argument against first generation genetic engineering (GMOs), which required crossing the "species barrier" through the transfer of genes from bacteria and other plant species. NBTs also allow researchers to more precisely and quickly insert desired traits from within species than traditional breeding, which is one reason why regulators look at them as a faster version of conventional breeding techniques. Due to these differences with GMOs, plants bred with these techniques have so far faced lower regulatory hurdles than "transgenic" products, although the regulatory landscape is unsettled.

NBTs occasionally use transgenics and most new products can be developed in a fraction of the time and cost of conventional or transgenic breeding. There is no finite set of NBTs and future techniques may be put under the same umbrella term. There are currently seven broad, scientific categories of NBTs. Most popular in agricultural biotechnology are gene editing—CRISPR systems and TALENs—and other NBTs, including RNA interference (RNAi) and epigenetic techniques and sprays.

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Gene or Genome Editing is a broad category that includes several techniques allowing scientists to do precise editing, including CRISPR. There are three gene-editing technologies:

- **ZFNs (Zinc Finger Nucleases)** is the oldest of the gene-editing technologies, developed in the 1990s and owned by Sangamo BioSciences. It has been primarily used in research for a variety of human diseases, including HIV/AIDS and hemophilia. It is used in plants to stimulate the cell's naturally occurring DNA repair processes, as an aid in mutagenesis and to enhance the efficiency of transgenic product development.
- **TALENs** (Transcription Activator-like Effector Nucleases), developed in 2009, offers an easier and more accurate method of gene editing. Its first reported success came in 2012 when researchers at Iowa State University used it to develop disease-resistant rice. TALENs result in a few "off-target"

effects. The technique has also been used to create hornless cattle (avoiding the painful dehorning practice used by many dairy farmers) and soybeans with higher quality oil.

- **CRISPR-Cas9 (Clustered Regulatory Interspaced Short Palindromic Repeats)** is the newest and most powerful of the gene-editing techniques. It is a natural bacterial defense system that scientists have "programmed" to target and edit DNA at precise locations. It offers researchers a relatively inexpensive, easy and quick option to engineer changes. CRISPR is akin to a "biological word processing" system or molecular scissors that allows scientists to snip away weaknesses or insert strengths already found in the species being developed. With CRISPR, researchers cut out a known, specific section of DNA. Then, one of two things happens: The loose ends are essentially glued back together, eliminating the undesired trait or weakness. Or a "repair" with a desired trait is inserted into the void.

CRISPR is being widely used in human disease research (Read Biotech 2.0 FAQ on Gene Editing), but there are few approved advances. The agricultural sector is further along. The USDA determined in April 2016 that it will not regulate a non-browning mushroom genetically modified using CRISPR–Cas9, making it the first CRISPR-edited product to receive a green light from the USDA.

Other NBTs include:

- **RNAi (RNA interference)** is a natural pathway involved in the regulation of gene expression, turning genes on and off. It works by attacking the messenger RNA that carries the instructions for the targeted genetic trait. RNAi has been used in several crops already, including the approved Arctic Apple and various Simplot Innate Potatoes. Scientists also have used RNAi to develop insect- and disease-resistant crops, crops that neutralize aflatoxin (dangerous to humans) and are exploring its use in targeting bee-killing varroa mites and other harmful insects. Bayer is working on an RNAi spray to combat weeds that have developed resistance to its glyphosate herbicide. The spray would neutralize the resistance in those weeds.
- **Agroinfiltration** is used to induce transient gene expression in plants or even in culture in plant cells, and is mostly confined to research or in production of drug proteins.
- **Epigenetic approaches** (such as RNA-directed DNA methylation) are being explored to manipulate plant DNA without permanently changing it. Modified crops such as soybeans, tomatoes and sorghum have shown increased yields and stress tolerance.
- **Site-directed mutagenesis** (aka oligonucleotide-directed mutagenesis) is a more targeted form of more random chemical or radiation mutagenesis—two techniques which have been in use since the 1930s and have resulted in some 3000 cultivars. It's now used mostly as an investigative tool.

What are some examples of gene edited products that have been approved for commercial use?

The first product to be approved by the USDA for commercial use was a non-browning mushroom in

2015. Developed by Yinong Yang, professor of plant pathology at Pennsylvania State University, the mushroom has still not been released commercially.

In 2016 Dupont Pioneer received a ruling of deregulated status for their new waxy corn, improved through CRISPR to improve stress tolerance. The number of products that have been cleared by the USDA is too numerous to list here, but they can viewed on the USDA APHIS website. The firm Calyxt alone has seven approved crops in the pipeline for production: high-fiber wheat, powdery mildew-resistant wheat, high-oleic / low-linoleic soybeans, improved quality alfalfa, cold storable potatoes, reduced browning potatoes and high-oleic soybeans. The high-oleic soybeans are the furthest along in commercialization. They were contracted by Calyxt to be planted on 16,000 acres on 75 farms in 2018.

The biotech company Cibus has released their herbicide-tolerant SU canola on a limited basis in Montana, North Dakota, Minnesota and Saskatchewan.

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How does the US government view the products of gene editing?

The first stop in the process of bringing a product of gene editing (PoGE) or other NBT is usually the USDA. Currently, the developer offers the USDA a description of the product and the techniques used.

The USDA then makes a determination as to whether they would consider the production to be regulated under their purview. The rationale underlying the USDA's ability to regulate many transgenic crops was the use of genetic material from bacteria and viruses deemed to be "plant pests" as vectors for introgressing novel genes into plant germplasm. Gene editing doesn't require the use of those vectors and doesn't necessarily leave behind any new genetic material from the vectors they do use. The USDA has announced that they don't feel they have the authority to regulate gene-edited crops, nor do they see a rationale if the crops could have clearly been bred via traditional methods over a longer time horizon. According to the USDA:

> Under its biotechnology regulations, USDA does not regulate or have any plans to regulate plants that could otherwise have been developed through traditional breeding techniques as long as they are not plant pests or developed using plant pests. This includes a set of new techniques that are increasingly being used by plant breeders to produce new plant varieties that are indistinguishable from those developed through traditional breeding methods. The newest of these methods, such as genome editing, expand traditional plant breeding tools because they can introduce new plant traits more quickly and precisely, potentially saving years or even decades in bringing needed new varieties to farmers.
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> "With this approach, USDA seeks to allow innovation when there is no risk present," said Secretary Perdue.

The EPA would be involved in regulating any new label of an herbicide paired with gene-edited herbicide-tolerant crops. The EPA also claims jurisdiction over insect- and disease-resistant crops where they could be construed as having Plant-Incorporated Protectants (PIPs). If and when somebody uses gene editing or another NBT to make a crop insect or disease resistant, the EPA will evaluate that product.

The regulation of gene-edited products by the FDA is more or less identical to that of the regulation of the products of genetic engineering. For crops, developers are strongly encouraged to submit materials such as compositional analysis for review or proceed to market at their own risk. No companies want to go to market vulnerable to charges from anti-GMO activists that a new food product hasn't been found to be safe by the FDA.

The picture is very different for gene-edited animals. Earlier this year the FDA ruled that they would regulate gene-edited animals as a new drug. We'll delve further into this process in future installment that looks solely at the regulation of biotech breeding of animals.

Marc Brazeau is the GLP's senior contributing writer focusing on agricultural biotechnology. He also is the editor of Food and Farm Discussion Lab. Follow him on Twitter @eatcookwrite