FDA approves hereditary blindness gene therapy

The US Food and Drug Administration (FDA) has given the go-ahead to Spark Therapeutics' gene therapy for treating biallelic RPE65-mutation-associated retinal dystrophy. The December 19 approval is the first gene therapy in the US to use an adeno-associated virus for delivery and the first for treating an inherited disease. Voretigene neparvovec, branded as Luxturna, received a unanimous vote of approval from an FDA advisory committee on October 12 (*Nat. Biotechnol.* **35**, 998, 2017). In concert with the milestone approval, the FDA announced that it is developing a policy framework for processing candidate gene therapies. "Next year, we'll begin issuing a suite of disease-specific guidance documents on the development of specific gene therapy products to lay out modern and more efficient parameters—including new clinical measures—for the evaluation and review of gene therapy for different high-priority diseases where the platform is being targeted," FDA Commissioner Scott Gottlieb said in a statement announcing the approval of Luxturna. Biallelic RPE65-mutation-associated retinal dystrophy affects an estimated 1,000–2,000 people in the US. The condition causes progressive sight impairment that leads to near total blindness in almost all patients. Luxturna is a one-time treatment. It is injected into the subretinal space where it delivers a functional copy of RPE65 cDNA to retinal pigment epithelial (RPE) cells, restoring the cells' ability to produce the key retinoid cycle enzyme all-*trans* retinyl ester isomerase. Spark Therapeutics announced that Luxturna will be available in the first quarter of 2018 from retinal surgeons trained by the company. Spark Therapeutics said it will announce pricing in early January. Industry estimates of the price range from $500,000 to $1.5 million, based partly on the $475,000 price tag for Novartis' adoptive chimeric antigen receptor (CAR)-T cell leukemia therapy Kymriah (tisagenlecleucel), which is also a one-time gene therapy treatment. The European Medicines Agency is reviewing Luxturna. Spark Therapeutics has gene therapies for treating hemophilia and neurodegenerative diseases in its pipeline.

"'We have to acknowledge quantitatively, it's the hardest thing we do as a society' and to do that society needs to engage and attract 'the rare geniuses' with appropriate recognition and reward." George D. Yancopoulos, CSO of Regeneron, commenting on the importance of innovative researchers to the biopharma industry at an industry summit in November. (*Forbes*, 30 November 2017)

With a free pass, CRISPR-edited plants reach market in record time

CRISPR–Cas9-edited plants can be cultivated and sold free from regulation, the US Department of Agriculture (USDA) is making increasingly clear. The agency gave a free pass to *Camelina sativa*, or false flax, with enhanced omega-3 oil. And more recently, in October, said that a drought-tolerant soybean variety developed with CRISPR falls outside of its regulatory purview. This *laissez faire* attitude from the agency shaves years and tens of millions of dollars off the cost of bringing a biotech plant to market. "It eliminates that huge barrier to entry for agbiotech companies," says Oliver Peoples, CEO of Woburn, Massachusetts–based Yield10 Bioscience (formerly Metabolix) which developed the camelina.

It would have taken Yield10 at least six years and $30–50 million to test and collect the data necessary to bring genetically engineered camelina through the full USDA regulatory process, says Peoples. "We did this in two years and [USDA's decision] took two months, and I assure you we didn't spend $30 million on it," he says. The company will present its technology to the US Food and Drug Administration's voluntary review process, he says.

Yield10's strategy is to allow CRISPR-Cas9 to make double-stranded breaks in the plant's DNA without a template to direct insertion of a specific DNA sequence. As a result, the plant's own repair mechanisms rejoin the DNA, giving rise to single-nucleotide inactivating insertions in all three copies of the target gene. Peoples would not disclose which gene his company manipulated in camelina.

Camelina oil is used as a biofuel and as a substitute for fish oil in aquaculture. Yield10 will likely make three or four additional edits to the plant line in order to boost camelina's oil content 25%, and translate the technology

Box 1 GM apples now in supermarkets: but how will the public react?

US grocery retailers on November 1 began selling genetically modified (GM) apples that resist browning, making them one of the first consumer-oriented biotech foods to reach the market. The apple's developer, Canadian firm Okanagan Specialty Fruits, a subsidiary of Germantown, Maryland–based Intrexon, is one of a few small companies to succeed in bringing a GM food all the way from discovery to retailers' shelves.

So far, the apples have appeared pre-sliced and packaged in stores in the US Midwest, Southeast and California. Their non-browning trait keeps them fresh-looking without the use of taste-altering preservatives. Okanagan achieved the effect by introducing a transgene to produce RNA designed to silence the expression of at least four browning polyphenol oxidase genes (*Nat. Biotechnol.* **33**, 326–327, 2015).

How have consumers reacted? About 60% say they are likely to buy GM non-browning apples, according to the company's pre-market consumer research, says Neal Carter, founder of Okanagan. Only about 10–15 % of consumers are staunchly against the product, he says, and some of those people change their minds after they've received more information about how the apples were engineered, or after tasting them. "When they get to experience the product, basically all the concerns about genetic engineering go away," Carter says.

Several apple grower associations previously raised concerns about Carter's product, saying it could disrupt the apple market and affect consumers' perception of the wholesomeness of apples. "It was the natural concern of an industry that has a product that is widely accepted to be so healthy," says Jim Bair, president of the US Apple Association in Falls Church, Virginia, an organization that had written to the USDA in 2011 asking it to reject GM apples. US Apple has since changed its position. "The regulatory agencies have confirmed that GM apples are identical to non-GM apples in nutrition, safety and wholesomeness, so consumers can buy and enjoy them without worry," Bair says. Apples are part of a healthy diet, so "anything that potentially expands the marketplace is going to be good for consumers."

Okanagan sells the sliced apples under the brand name "Arctic," and will not label them as GM. Instead, a smartphone-scannable QR code on the bag takes consumers to a website with more information. US regulators approved Okanagan's first apple varieties—Golden Delicious and Granny Smith—in February 2015, and Canadian regulators did the same a month later. *EW*

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Camelina or false flax is grown as an oilseed crop to produce vegetable oil and animal feed.

to other oilseed crops such as canola and soybean.

The edited camelina and the drought-tolerant soybean developed by scientists at USDA's research arm are two of at least five CRISPR–Cas9-edited organisms to sidestep USDA's regulatory system in the last two years (**Table 1**). The first such plant to come before the agency, a CRISPR–Cas9-edited white button mushroom (*Agaricus bisporus*), modified to resist browning, received a free pass in April 2016 (*Nature* **532**, 293, 2016).

Plants modified using other gene-editing techniques, such as transcription activator-like effector nuclease (TALEN) and zinc-finger nuclease (ZFN) systems, can also fall outside of USDA's authority (*Nat. Biotechnol.* **30**, 215–217, 2012). The agency in September said it would not regulate a TALEN-edited alfalfa variety with improved nutritional quality. Calyxt (formerly Cellectis Plant Sciences) in New Brighton, Minnesota, developed the crop.

The USDA's change in attitude toward genetic engineering came with the arrival of new technologies to modify plants. Unlike transgenic plants modified using older technologies (**Box 1**), plants modified with CRISPR–Cas9 and other new gene editing techniques do not require USDA oversight because the resulting plants don't contain DNA from "plant pests" such as viruses or bacteria. Such organisms were a necessary component in early plant modification tools, such as *Agrobacterium*-mediated transformation, and triggered regulatory oversight when the US government in the 1980s and 1990s wrote its framework for regulating biotech crops. Although the USDA recently reviewed the old biotech framework, so far, the agency has not broadened the regulatory net to catch organisms made with the newer techniques (*Nat. Biotechnol.* **33**, 1221–1222, 2015).

Companies that want to know whether their engineered organisms fall outside the USDA's purview can submit their enquires through the agency's "Am I Regulated?" route. In all, the USDA has received at least 57 inquires over the past seven years from organizations large and small—from ag giant Bayer to the startup BioGlow—and in most cases has granted the firms a free pass.

One such firm is Calyxt, which holds six TALEN-edited crops with non-regulated status, in its pipeline. That includes a high oleic soybean variety that produces oil with increased shelf life and frying characteristics without the need for partial hydrogenation—a process that pumps into food unsaturated trans fats. The company generated the trait by a nucleotide deletion to disrupt two fatty acid desaturase genes called *FAD2* and *FAD3*. Calyxt plans to commercialize the product in late 2018, according to a spokesperson for the company.

Lawn and garden company Scotts Miracle-Gro, in Marysville Ohio, submitted four such inquires related to turf grasses genetically engineered to grow shorter and thicker and tolerate glyphosate (*Nat. Biotechnol.* **33**, 223, 2015) and received non-regulated status for all four. The company is continuing to test and develop two of those: Kentucky Bluegrass and St. Augustine grass engineered to grow more slowly so that they require less mowing, says Bob Harriman, vice president of biotech at Scotts. The company transformed the plants using a gene gun and DNA sequences from non-plant pests.

While the regulatory route for CRISPR-edited plants may be getting streamlined, the road to intellectual property licensing remains rather hazy. One recent deal may help define the playing field. The Broad Institute in Cambridge, Massachusetts, and DuPont Pioneer, a division of DowDuPont, which hold key CRISPR patents, said in October they had come to an agreement that will allow companies to obtain a non-exclusive license, while making the intellectual property free for universities and non-profit organizations.

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Table 1 CRISPR-edited plants in the pipeline that USDA will not oversee

Date of USDA response	Inquiring institution (location)	Plant trait engineered with CRISPR–Cas9
10/16/2017	USDA ARS, Plant Science Research Unit (St. Paul, Minnesota)	Soybean (*Glycine max)* with drought and salt tolerance; achieved by disrupting the *Drb2a* and *Drb2b* genes (double-stranded RNA-binding protein2 genes)
8/29/2017	Yield10 Bioscience (Woburn, Massachusetts)	Camelina with increased oil content; target genes not disclosed
4/07/2017	Donald Danforth Plant Science Center (St. Louis)	*Setaria viridis*, or green bristlegrass, with delayed flowering time; achieved by deactivating the *S. viridis* homolog of the *Zea mays* ID1 gene
4/18/2016	DuPont Pioneer (Johnston, Iowa)	Waxy corn with starch composed exclusively of amylopectin; achieved by inactivating the endogenous waxy gene *Wx1* that encodes a granule-bound start synthase catalyzing production of amylose
4/13/2016	The Pennsylvania State University (University Park, Pennsylvania)	White button mushroom *(Agaricus bisporus)* with anti-browning properties; achieved by knocking out a gene coding for polyphenol oxidase (*PPO*)

Source: USDA