First US approval for a transgenic animal drug

The animal biotech sector reached a landmark in February when the US Food and Drug Administration (FDA) announced the approval of ATryn, an anticoagulant protein derived from the milk of transgenic goats. Although the product had previously been approved in Europe, GTC Biotherapeutics of Framingham, Massachusetts, is the first company to have a transgenic animal drug approved for US use.

So far, 2009 has been a good year for animal biotech companies. ATryn's approval follows closely on the heels of the FDA final guidance issued a month earlier that describes the regulatory path for transgenic animals and their products for both healthcare and food production. The timing of the announcements provides a welcome boost to an industry that has long been struggling in the US because of the lack of a clear regulatory framework and low investment levels.

ATryn, a recombinant human antithrombin-α produced in transgenic goats' milk, validates "the regulatory process they [FDA] just codified in the guidance," says Barbara Glenn, who is managing director for animal biotech at the Biotechnology Industry Organization in Washington, DC.

The FDA's recently issued regulatory framework, years in the making, is the first US government guidance for transgenic animals. It oversees all such animals, whether used as bioreactors to produce proteins and replacement tissues for therapeutic/industrial uses or modified for improved nutritional status, disease resistance or faster growth (*Nat. Biotechnol.* **26**, 1205–1207, 2008). The agency's experience with ATryn manufacturers GTC Biotherapeutics and other animal biotech companies has helped shape the approval pathway into its final form.

Milk from GTC's transgenic goats pictured here will be used to produce ATryn, the first animal drug to be approved in the US.

ATryn was approved in the European Union (EU) in 2006 on the basis of a phase 2 study of 13 people and compassionate use in another 5. But the FDA required an additional phase 3 study, says Tom Newberry, vice president of corporate relations at

SELECTED research collaborations

Partner 1	Partner 2	$ (millions)
Epistem (Manchester, UK)	Novartis (Basel)	49
Xencor (Monrovia, California)	Pfizer (New York)	*
Syngenta (Basel)	Anhui Rice Research Institute (Anhui, China)	*

* Not disclosed

GTC. The primary endpoint for this new trial was the incidence of thromboembolism in 31 individuals (14 of whom came from the European trial, with 17 supplementary patients) with hereditary antithrombin deficiency who received ATryn for one week to prevent thromboembolism before, during or after surgery or childbirth compared with plasma-derived antithrombin-treated controls. Only one of the ATryn-treated participants developed a thromboembolus. Pooling the phase 3 and phase 2 data in a noninferiority trial design, the FDA accepted that ATryn was as effective as plasma-derived antithrombin-α.

The transgenic animal–produced protein is unlikely to be a financial windfall for GTC, however. ATryn is indicated for use in people with hereditary antithrombin deficiency, who are at high risk of blood clots during surgery and childbirth. Rodman and Renshaw of New York estimate that about 1,500 surgeries in the US and 3,500 in Europe require antithrombin therapy, and project a peak of $40–50 million annually in the US, perhaps double that worldwide. The firm predicts sales of $6–10 million in 2009. "It's not a game changer the second it comes out on the market, and I think it's going to take some time [to become accepted]. It hasn't had meaningful sales in Europe," says Reni Benjamin, managing director and senior biotech analyst with the firm, who admits that lagging sales in Europe might be due to insufficient marketing. "We want to see how well [GTC's partner, Ovation] will do at generating sales." Ovation Pharmaceuticals of Deerfield, Illinois, which was acquired by Danish pharma company H. Lundbeck of Copenhagen in February, has marketing rights to ATryn in the US.

ATryn will compete against a human plasma version of Thrombate III (antithrombin III), marketed by Talecris Biotherapeutics, located in Research Triangle Park, North Carolina. Thrombate III's efficacy is the same, says Benjamin, but the use of transgenic goats could make ATryn cheaper to produce. Human plasma products can also be a source of blood-borne diseases. Using transgenic goats "obviates that risk," says Benjamin.

GTC is also pursuing ATryn as a treatment for cases of heparin resistance. Individuals undergoing cardiopulmonary bypass are given heparin to prevent clotting during the procedure, but antithrombin can become depressed, blunting the drug's effectiveness. The company believes that supplementary ATryn could help restore antithrombin levels and circumvent heparin resistance. "That would be a much larger market," says Newberry.

The approval represents a first step for GTC, which will seek to apply its proprietary technology to the production of other drugs. "The value is in the proof and acceptance of their *in vivo* platform to produce therapeutic proteins," says Eric W. Overström, a professor of biology and biotech at Worcester Polytechnic Institute, in Worcester, Massachusetts, who collaborated with GTC on some of the original goat transgenic work but is no longer associated with the company.

GTC achieves expression of ATryn in milk by linking the antithrombin-α transgene to mammary-specific promoters of milk

Details

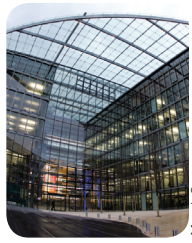
The companies have entered a collaboration to identify new drug targets and therapeutics across various disease areas. Under the terms of the agreement, Novartis will pay Epistem, a company commercializing its expertise in epithelial stem cells, $4 million up front and two years' worth of R&D support. Novartis has an option to exclusively license targets for biotherapeutic product development in exchange for license fees, milestone payments and royalties. The deal also includes up to $45 million in milestones for each new product developed. Epistem is also eligible to receive tiered royalties on global sales. Epistem's internal research, focused on the regulation of adult stem cells in epithelial tissues including gastrointestinal tract, skin, hair follicles, breast and prostate, will benefit from the pact.

Pfizer has agreed to license and evaluate Xencor's antibody optimization technologies. Pfizer will apply Xencor's Xtend technology to prolong antibody half-life and XmAb ADCC—enhancing technology to its antibody drug candidates in several discovery projects. Pfizer has also taken a commercial license for Xencor's technology for one program. Xencor will receive an up-front payment and is eligible to receive additional considerations based on the successful commercialization of products that incorporate its technologies.

The eight-year collaboration program will focus on drought tolerance and nitrogen utilization optimization in key crops such as corn and soybean (but the base crop of the project is obviously rice). ARRI researchers will use rice as a model to study novel gene functions, and will work closely with Syngenta's new biotech research and technology center in Beijing.

IN brief

RIP Raptiva?


Merck Serono

Merck Serono headquarters

The US Food and Drug Administration has issued a public health advisory on Genentech's psoriasis drug Raptiva following four cases and three confirmed deaths from progressive multifocal leukoencephalopathy (PML), a rare and usually fatal brain viral infection, in patients taking the drug for several years. In Europe and Canada, where the drug is marketed by Geneva-based Merck Serono and Serono of Mississauga, Ontario, respectively, regulators have taken Raptiva off the market, stating that the benefit did not justify the risk. This may be the last straw for Raptiva (efalizumab), a monoclonal antibody (mAb) directed against T-cell marker CD-11. "It's doomed," says Eric Schmidt, biotech analyst with Cowen and Company of New York. Raptiva, developed by Genentech of S. San Francisco, California, received a black box warning in 2005, after several cases of hemolytic anemia and again, in October 2008, following the first PML case. "Fortunately for Genentech it's a minor drug," garnering around $100 million annually, says Schmidt. Although Raptiva was the first biologic to reach the market for psoriasis, sales were quickly eclipsed by a trio of tumor necrosis factor-α inhibitors: Enbrel (etanercept) from Amgen of Thousand Oaks, California, Remicade (infliximab), from Centocor of Horsham, Pennsylvania and Humira (adalimumab), from Abbott of Abbott Park, Illinois. Centocor's mAb Stelara (ustekinumab), which targets IL-12 and IL-23, and recently approved in Europe, may further erode Raptiva's sales. This isn't the first time an immune modulating drug has been associated with PML. In 2005, the multiple sclerosis drug Tysabri (natalizumab) produced by Biogen-Idec of Cambridge, Massachusetts, and Elan of Dublin, a mAb targeting integrin, was voluntarily withdrawn from the market after two patients contracted PML; the companies later returned with a risk minimization plan. Whereas over 46,000 patients have taken Raptiva, only roughly 1,000 have been taking it for three years, hence the incidence of PML with Raptiva may be higher than with Tysabri (1 in 15,000). Michael Paranzino, head of the Psoriasis Cure Now of Kensington, Maryland, feels that banning Raptiva isn't warranted, especially as market leader Enbrel only relieves 50% of patients. "Before a ban, why not consider restrictions on continuous, multi-year use? Why not consider having it as a second- or third-try option if the experts are convinced there are other, first-line options that are safer?" According to senior manager at Genentech, Tara Cooper, the company is working with the FDA, possibly to develop a risk minimization plan. *Laura DeFrancesco*

IN brief

EU impasse over GM deepens

Austria and Hungary have asserted their right to ban cultivation of a genetically modified (GM) corn, known as MON810. On March 2, an overwhelming majority of environment ministers rejected the European Commission's initiative to order these member states to adhere to European Union legislation and lift their national bans on planting the GM maize. MON810 is an insect-resistant corn engineered by Monsanto and the only GM product approved for growing in Europe. It is cultivated in Spain, Czech Republic, Romania, Portugal, Germany, Poland and Slovakia. But after the recent vote, it now seems likely that when the council of ministers next meets in June, it will uphold similar bans currently in place in France and Greece, intensifying the disarray. "By failing to defend the EU approval system European governments undermine public trust. Why make tough laws on GM crops and then break them?" asks Nathalie Moll, spokesperson for the association of bioindustries EuropaBio. Things will deteriorate further if Germany confirms statements released by its ministers of environment and agriculture Sigmar Gabriel and Ilse Aigner that Berlin is considering a cultivation ban. In February, an EU regulatory committee deadlocked over whether to allow planting of two other insect-resistant maize lines, BT-11 and 1507. Final approval will now depend on the council of ministers and, in case of stalemate, on the Commission. A more propitious wind blows in Asia, where Monsanto has started field trials of GM corn in India and is eyeing Indonesia next. *Anna Meldolesi*

Cellulosic ethanol stimulus

Young companies are likely to benefit from the $1.3 billion earmarked for cellulosic fuel projects in the US stimulus package. The bill, passed in February, gives the US Department of Energy (DOE) up to $500 million to spend on loan guarantees for experimental biofuel facilities and $800 million for research projects spanning "the whole range of biomass development," says Christina Kielich, a DOE spokesperson. The agency says it will put scientists to work finding new ways to break down cellulosic feedstocks—like switchgrass and woodchips—into chemical compounds, convert the compounds into fuels and address feedstock sustainability. The funding may help more startups get off the ground but isn't nearly enough to transform the fuel industry, say biofuel experts. "The government will need to come up with an energy bill that funds innovation more comprehensively," says David Aldous, CEO of Range Fuels, a cellulosic biofuel company in Broomfield, Colorado. Aldous points to Brazil's ethanol program in the 1970s, which financed the development of ethanol-only cars, guaranteed ethanol purchases and loans, fixed prices and mandated ethanol blending with gasoline. "It's that kind of commitment that transforms a country," he says. Indeed, US regulators may soon increase the blend rate for ethanol in gasoline to 13% from 10%, according to the Governors' Biofuels Coalition. *Emily Waltz*

proteins. The original ATryn-producing goats were developed by microinjection, but animals currently used for production have been bred by nuclear transfer. The cloning technique allows production to be ramped up as all animals carried to term will be transgenic, says Newberry.

Transgenic animals could prove useful for producing proteins that are difficult to manufacture using traditional recombinant systems, such as plasma proteins. GTC hopes to apply its goat transgenic technology to produce clotting factors VIIa, IX and VIII, the missing protein in type A hemophilia. Other commercial targets include monoclonal antibodies (mAbs) and biogenerics. In February, for example, GTC announced that it had entered into collaboration with Ruakura, New Zealand–based AgResearch to develop transgenic founder animals for the production of two follow-on biologic mAbs.

The transgenic system lends itself to proteins that need to be produced in large volumes, such as mAbs, because it can reduce manufacturing costs by an order of magnitude, according to Newberry. This could be critical for the production of biogenerics, which will likely be required to undergo expensive clinical trials to show therapeutic equivalence to the innovator product. A transgenic animal production system could lower manufacturing costs enough to reduce the final cost substantially.

Others hope to replicate GTC's early success. PharmAthene of Annapolis, Maryland, is also working on transgenic goat milk, whereas Pharming, a company in Leiden, The Netherlands, is developing rabbit milk as a protein production system. Technical barriers have been largely overcome. "Nowadays there is a whole variety of ways to generate transgenic animals, and the behavior of transgenes is pretty well known. You can't always predict what's going to happen [to an introduced gene], but given enough founder animals, you can almost always get what you want at the end of the day," says Bob Wall, research physiologist at the US Department of Agriculture's Agricultural Research Service, in Beltsville, Maryland.

One issue for protein production has been surface glycosylation, which can affect a protein's therapeutic potential and immunogenicity. Glycosylation in goats (and in cows and sheep) typically involves *N*-glycolylneuraminic acid, a monomer virtually absent in native human proteins, whereas rabbits and chickens contain oligosaccharides (containing *N*-acetylneuraminic acid) that resemble those in humans. But ATryn's approval in Europe and now in the US is a sign that these differences will not pose insurmountable regulatory hurdles. "Early on in the development of bioreactor animals [different glycosylation and post-translational modification profiles] had sort of surprised and concerned the sponsors of these projects, but given that we now have a product on the market in the states in Europe, I guess that's not an issue," Wall says.

Most are confident that these developments herald a new era for transgenic animal development in the US. "I think there hasn't been as much activity in the US as in Europe, in part because industry hasn't gotten a clear sign from FDA as to how these products will be regulated. I think that's one of the pressures that FDA felt in realizing they needed to put out a guidance," says Sheldon Bradshaw, a former chief counsel of the FDA and now a partner at Hunton & Williams LLP in Richmond, Virginia.

FDA's guidance has been years in the making and many believe that the uncertainty took a toll on the US animal biotech industry. The delay may have been natural, given the novelty of the technology. It took FDA some time to decide exactly how to regulate the products from a transgenic animal and the agency ultimately decided to classify the transgene product as a drug and to regulate it as such. "It has been a long evolution with respect to determining that, and then achieving coordination between its centers and bringing forward [the guidelines] on paper," says Glenn.

But recent developments have made Glenn more upbeat. The lack of guidance "had the potential to (affect) the industry's viability in the US. It didn't come as soon as we wanted it, but we're on a positive path right now."

Jim Kling *Bellingham, Washington*

IN their words

"This is cosmetic medicine. Others are frightened by the criticism but we have no problems with it."

Jeff Steinberg, director of the clinic Fertility Institutes, on the advertisements on their website offering to screen embryos for gender, eye color, hair color and complexion. (*Wall Street Journal*, February 12, 2009)