Belated approval of first recombinant protein from animal

In June, the London-based European Medicines Agency (EMEA) announced approval of the first drug produced in an animal bioreactor: GTC Biotherapeutics' ATryn, four months after its initial rejection. The drug—a recombinant form of human antithrombin produced in goats—prevents blood clots in patients who lack the natural anticoagulant protein. Industry insiders believe that EMEA altered its position, after a more detailed review of the data, because it wanted to convey its support to industry for this bioprocessing method.

EMEA's positive opinion, announced on June 2, 2006, overturns the agency's rejection of ATryn last February. Atryn is indicated for hereditary antithrombin deficiency, a rare disease afflicting just one in 3,000–5,000 people. So when GTC first approached the EMEA, it could provide clinical data on just 19 cases—five surgical patients, nine pregnant women and five 'compassionate use' cases. Citing dosing inconsistencies, the EMEA disqualified all but the five surgical cases, leaving a number far below the minimum 12 cases required for its review. EMEA also claimed GTC hadn't sufficiently considered antibody stimulation, which might be induced by foreign elements on the transgenic protein.

After the first rejection, GTC dusted itself off and assembled a panel of hematologists who, together with EMEA's own experts, reviewed the data and concluded that ATryn was safe, and its efficacy similar in both pregnant and nonpregnant patients. Thus assured, EMEA returned the pregnancy cases to the data set, and approved ATryn on the condition that GTC monitor clinical uses for antibody reactions. "We were able to show the safety risks were lower than the benefits of efficacy and that's how you get drugs approved," said Tom Newberry, GTC's vice president for corporate communications.

The first recombinant protein produced in goat bioreactor Atryn received a belated approval from the European Union in June after an initial rejection.

ATryn's approval gives a welcome boost to this industry sector, said Phillip Nadeau, a biotech analyst with Cowen & Co. in New York. "Before this decision, pessimists believed regulatory authorities would always find a way to shoot down transgenic proteins," he said. "But now that we have an approval, that argument goes away."

Although he won't disagree, Louis Marie Houdebine, director of the animal gene study laboratory at the French Institute for Agronomy Research and a cofounder of BioProteins Therapeutics, suggests EMEA may have also been motivated to push an animal-derived transgenic protein through the regulatory process. "It's possible that given ATryn's low risk and infrequent use, EMEA chose to give an agreement that could have a significant impact on the development of processes to prepare recombinant pharmaceutical proteins," he says. "They want good proteins and they hope the method will work."

EMEA officials wouldn't comment. But the agency's positive opinion was immediately reflected in GTC's stock value, which jumped by more than 20%. The stock of GTC's closest competitor—Pharming, a Dutch company working with rabbits—rose nearly 10%, reflecting a broader impact on investor confidence. "It really confirms the regulator's validation of the technology," says Samir Sinjh, Pharming's chief business officer. Sinjh also emphasizes that regulators respond more favorably to transgenic proteins developed for unmet needs.

The sector still faces some difficult challenges, however. Regulatory agencies, Sinjh stresses, need assurance that transgenic proteins are safe, and this creates burdensome data requirements. The biggest safety concerns, according to Amy Rosenberg, supervisory medical officer with the US Food and Drug Administration's (FDA) Center for Drug Evaluation and Research, fall into four categories: infection (including prion infection for transgenics made in cattle); allergenic responses, immunogenic responses and autoimmune reactions arising should transgenic proteins break tolerance to their endogenous, self-protein counterparts. "We would really need assurance that the animals aren't infected with any kind of prion disease," she says. "And each product poses its own unique risk—for instance, recombinant versions of endogenous proteins might pose immunogenicity risks that you might not encounter if the protein doesn't have a human counterpart."

Sinjh says it's incumbent on researchers to safeguard their animals from infection, not just by genetic characterization, but also by appropriate feed, environment and physical contact with other animals. "But all these animals are in contained facilities," he says. "And everything is monitored, so we think there's a very low risk of transferring infectious agents [to transgenic proteins]."

FDA officials interviewed for this article agreed, noting many of the safety risks posed by animal bioreactors also arise with other production methods. For instance, therapeutic proteins are made with mouse and yeast cells, and culture media often contain fetal calf serum, providing ample opportunity for exposure to non-human elements. "I don't see any show stoppers for these kinds of products," says Basil Golding, director of the division of Hematology at FDA's Center for Biologics Evaluation and Research. "Provided good manufacturing practices are followed, the products would be approved if the studies met certain requirements of safety and efficacy."

Charlie Schmidt, Portland, Maine

Table 1 Selected products currently in development for production in animal bioreactors

Company	Product (bioreactor)	Indication	Development stage
GTC Biotherapeutics (Framingham, MA, USA)	Recombinant human antithrombin, ATryn (goat)	Hereditary antithrombin deficiency	Approved in EU; phase 3 in US
Pharming (Leiden, The Netherlands)	C1 inhibitor (rabbit) Human lactoferrin (rabbit) Human fibrinogen (rabbit)	Hereditary angiodema Infection and inflammation Tissue sealant	Phase 3 Preclinical Preclinical
BioProtein Technologies (Paris)	Rotavirus virus-like particles (rabbit)	Rotovirus infection vaccine	Preclinical
PharmAthene	Version of human butyrylcholinesterase (BChE), Protexia (goat)	Treatment for chemical nerve agents	Preclinical

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