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that isn't the problem, says ZymoGenetics chief executive Bruce Carter. Rather, it is because the acute hospitals that use thrombin (for hemostasis in surgery) have a convoluted and lengthy procedure for switching between preferred therapeutics. "Like other recombinant proteins, it is going to take time," says Carter. Meanwhile, companies like King are constantly improving their animal products, for example by removing components like bovine factor V, suspected of causing immunological reactions in patients.

Another problem may be difficulty in proving equivalent efficacy. One example is Altus Pharmaceuticals of Cambridge, Massachusetts, which in August announced the results of its phase 3 study with the enzyme replacement therapy Trizytek for cystic fibrosis–related pancreatic insufficiency. On average, the drug met its primary endpoint, but the level of efficacy shown by the trial was disappointing. For some non-US subjects, the recombinant microbe-derived enzyme produced no response beyond placebo, whereas the porcine-derived enzyme replacement therapies—Trizytek's competing products—showed no such limitation. The announcement slashed Altos' share price by half, as analysts questioned whether the FDA's preference for non-animal-based products will be sufficient to get Trizytek regulatory approval without further trials, despite its weak showing.

The pros and cons of recombinants vary from protein to protein, says Genzyme's Edmunds. "Even commodity proteins, such as serum albumin, can be produced [as a recombinant version] in large quantities using transgenic animals, as GTC Therapeutics [of Framingham, Massachusetts] does," he points out.

Other experts agree. "There is no simple or single explanation for recombinants' limited success in some markets," says David Glover, an immunotherapeutics expert based in Newmarket, UK. "The cost differential between recombinants and blood products can be huge and, for some customers, may not be justified by the minor advantages offered by recombinants."

Glover, formerly a medical director of the British immunotherapeutics company Cambridge Antibody Technology, since acquired by London-based AstraZeneca, notes that many therapeutic proteins offer a limited commercial opportunity. "The financial return on the investment needed to create recombinants may not be sufficient," he says. That, he says, is why Cambridge Antibody Technology passed on the opportunity to make human recombinant antibody replacement products for various immunoglobulin products against some common viral diseases, antidotes to drugs and poisons and antivenoms for specific snake or spider bites. As a result, the only treatment for some of these indications is still sheep antibodies or even horse serum.

The key dynamic for the future is the increasing caution of the regulators. Last October, the FDA told manufacturers of porcine-derived pancreatic enzyme replacement therapies to start preparing new drug applications by April 2008, leading to either approval by April 2010 or removal of their products from the market.

Two sad episodes from the 1980s and 1990s are engraved on doctors' and regulators' consciousness, notes Glover. Children were infected with Creutzfeldt-Jakob disease as a result of being given human growth hormone extracted from cadaver brains; and hemophiliacs were infected with HIV after receiving factor VIII clotting agent taken from pooled plasma donations. Both of these triggered a general market switch from natural products to the recombinant alternative.

Nowadays, pooled or natural human products are much more extensively filtered, purified and tested than they used to be. "But there is always the risk that a previously unknown infective agent, such as a new prion or viral disease, might sneak through before a test was developed to detect it," says Glover. Quite apart from unknown pathogens, there are still many relatively common viruses that are not routinely tested, including West Nile and Japanese encephalitis, as well as rare but very dangerous viruses like Ebola.

The danger of prions is particularly worrying after recent research by a group led by Claudio Soto of the University of Texas in Austin, Texas. Soto and his coworkers found that mixing infectious prions from one species with normal prion proteins from another can create new strains of infectious proteins (*Cell* **134**, 757–768, 2008).

Soto's findings prove that cross-species transmission of proteins could generate numerous infectious foldings of a prion protein—implying a very large 'universe' of possible prions. Some of which, he notes, with likely "dramatic effects." Soto acknowledges that the new findings have "worrisome" implications for the use of animal-derived medical products: "Prions are very sticky and difficult to eliminate, and indeed can be concentrated upon purification of other products." What regulators will make of this, though, he is unwilling to predict: "Their decisions are influenced by political and economic issues as well as science," he says.

To some, it seems that nothing short of another major contamination scare—probably involving the prion disease bovine spongiform encephalopathy—will force the pace of change.

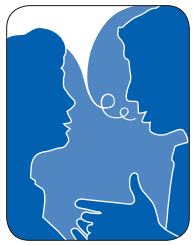
Peter Mitchell *London*

IN brief

Tysabri's troubles return

Two new cases of progressive multifocal leukoencephalopathy (PML) in patients treated with Tysabri (natalizumab) reported in July have increased uncertainty over the multiple sclerosis drug's prospects. Few, however, believe Tysabri will be pulled from the market as it was in February 2005 when three people developed the rare, viral-induced disease (*Nat. Biotechnol.* **23**, 397–398, 2005). In 2006, Tysabri returned to the US market and was approved for use in the EU (*Nat. Biotechnol.* **24**, 874, 2006) under controlled access plans designed to promote early detection of PML. Though touted as a potential blockbuster, the renewed safety concerns mean Tysabri may not achieve the commercial success hoped for by Cambridge, Massachusetts–based Biogen Idec and its marketing partner Elan of Dublin. The two latest patients to develop PML—both in the EU—were using Tysabri alone, in contrast to earlier cases seen in combination trials of Tysabri with Avonex (interferon β-1a). "This is a little bit of a splash of cold water in the face," says Clyde Markowitz, director of the Multiple Sclerosis Center at the University of Pennsylvania, Philadelphia. "A lot of people felt that the combination of therapies may have been responsible." August brought Biogen more bad news, when a federal judge refused to transfer a lawsuit over a patient's death from a Boston court to a federal court in Iowa. Biogen and Elan argued that it should be moved to federal court to resolve whether the US Food and Drug Administration's approval shields drug makers from lawsuits. *–Hannah Hoag*

IN their words



"We've decided to eliminate our corporate aviation group as part of our continuous improvement efforts…."

Bristol-Myers Squibb's Sonia Choi puts a positive spin on the company's decision to sell four aircraft and dismiss 32 employees to cut costs. (*The Times, Trenton*, September 3, 2008)

"We believe you are offering a high-risk test that has not received adequate clinical validation, and may harm the public health."

An FDA warning letter sent to LabCorp concerning their OvaSure homebrew Luminex immunoassay that predicts ovarian cancer on the basis of six protein biomarkers. (*Los Angeles Times*, September 16, 2008)

"Drug DTC has now gone QVC."

Mike Huckman on Merck's (Whitehouse Station, New Jersey) new line of Gardasil jewelry similar to that advertised on shopping network QVC. (*Seeking Alpha*, August 27, 2008).