IN brief

Joint inspections still cool

Regulatory agencies on both sides of the Atlantic, the European Medicines Agency (EMA) and US Food and Drug Administration (FDA), are urging companies to apply to its joint good manufacturing practice (GMP) inspections because, since its launch in August 2009, the program has had a slow uptake. The regulators aim to increase the number of sites inspected and avoid duplication. But the advantages to companies may be elusive. "Biopharma and API [active pharmaceutical ingredients] manufacturers are undergoing audits and inspections, almost weekly, and this auditing burden is likely to increase under new proposals announced by the FDA in June," says Hedley Rees, founder and CEO of Biotech PharmaFlow, a UK-based, supply-chain management company. To qualify for the joint inspection, companies must have submitted marketing authorization applications in parallel to both the EMA and the FDA, or be hosting a single joint routine reinspection. But these requirements are such that the advantages are lost on would-be applicants. "There are also ingrained cultural differences between the FDA and EMA inspections, with wide variations in requirements and interpretation," adds Rees. "Companies perceive that having a joint inspection will simply raise twice as many issues, leading to negotiations with two parties and the production of two separate reports." *Suzanne Elvidge*

Stimulus trickle

Private biotech companies have received only a small fraction of the $10 billion from the American Recovery and Reinvestment Act (ARRA) of 2009 funds intended for biomedical research. In fiscal year 2010 the National Health Institute awarded $196 million dollars of stimulus funding to for-profit organizations, representing 4.2% of the total ARRA funding that passed through the National Institutes of Health (NIH)'s Office of Extramural Affairs, this despite the federal investment's goal of promoting innovation and economic growth in the biopharma sector (*Nat. Biotechnol.* **27**, 587, 2009). Ellen Dadisman, managing director of communications at the Washington, DC–based Biotechnology Industry Organization (BIO), reasons that this trend is consistent with the NIH's intention to direct awards toward basic research. As BIO members are usually focused on translational technologies, so it seems reasonable that they would receive a minor part of the stimulus funding, says Dadisman. "It is our hope that there will be more opportunities for translational/company grants," Dadisman adds, stressing that small companies can receive government funding by other channels, such as Small Business Innovation Research and Small Business Technology Transfer schemes. Additionally, the awards were sometimes announced with very short notice, limiting the number of applicants that could be ready in time. The ARRA Challenge Grants, for example, were announced on 4 March 2009, and had an application closing date of 7 April 2009. *Nidhi Subbaraman*

cleared the way for TKT, which had secured marketing approval for Dynepo (amphetamine and dextroamphetamine) in Europe in 2002, to start looking for a partner to commercialize the product. It was this search that led it into the arms of Shire, then a specialty pharmaceutical company, best known for Adderall, a treatment for attention deficit hyperactivity disorder.

In the event, rather than licensing Dynepo, Shire bought the whole of TKT for $1.6 billion in 2005.

These disputes over whether human proteins produced by gene-activation infringed the rights of those producing versions of the same proteins through recombinant means are now the stuff of biotech lore. One person who experienced the saga from end to end, including giving evidence about the gene-activation technology in court, is Mike Heartlein, vice president of R&D at Shire Genetic Therapies, who joined TKT in 1989.

Looking back from the perspective of having products on the market, Heartlein says, "It is gratifying when you start with a basic technology and see it develop all the way through the laboratory phase, into the clinic and onto the market."

Heartlein says gene activation can potentially turn on any endogenous gene. In the ten genes activated to date, Shire has in each case used the same DNA promoter. The company has applied homologous recombination to develop other promoters, and Heartlein says there is a continuing research program looking to optimize gene expression. To date, however, no other promoter has proven better than the original.

As a result, gene activation has yet to provide clear advantages in terms of manufacturing, Heartlein says. "That was one of the early promises of the technology—it remains that: the promise has not translated, but it may do so as we discover stronger promoters that augment gene expression," he adds. Heartlein is not really aware of any difference between manufacturing proteins in gene-activated and recombinant cell lines because Shire has never done a direct comparison.

Alongside its effort on promoters, Shire has also done extensive work on the human cell line HT10-80 from the American Type Culture Collection, in which it manufactures its proteins. "We have spent five to six years around converting those cells to make them appropriate for processing in bioreactors," Heartlein notes.

Overall, though, as there is little to choose between gene-activated and recombinant cell lines in terms of manufacturing efficiency, Shire is agnostic about which technology it uses; indeed, Elaprase (idursulfase), its treatment for Hunter syndrome/mucopolysaccharidosis, which was approved by the FDA in 2006, uses recombinant technology in a human cell line.

Proteins generated by means of gene activation may present advantages, however, in terms of safety and efficacy. Apart from having exactly the same amino acid sequence as the natural product, gene-activation products also have identical glycosylation patterns, a property that is expected to have clinical implications. In November 2007, Shire published work showing that Dynepo has less pronounced angiogenic properties than Aranesp (darbepoetin alfa) *in vitro*. The researchers, led by Alan Stitt at the Centre for Vision and Vascular Science, Queen's University, Belfast, concluded this could be associated with the different glycosylation patterns of the two products.

David Buck, analyst at Buckingham Research Group, in New York, points out that Shire's unique way of manufacturing protein drugs for rare diseases "leads to what [appear] to be advantages in terms of shorter infusion times and less immunogenicity."

"In the clinic, particularly for Gaucher, we've not seen antibodies develop against our product, [which are sometimes] seen with Cerezyme," Heartlein says. "That's exactly what you would predict in terms of immunogenicity."

Buckingham Group's Buck believes gene-activation provides Shire with a strategic advantage, at least "to some extent." In addition, he says the boot may now be on the other foot with Shire, as the company may be able "to block generic versions in future, though it's not something they have played up."

Now other approaches to turning genes on and off, or otherwise modulating endogenous genes, are opening up, notes David Sourdive, executive vice president of corporate development at Cellectis of Paris, a specialist in genome engineering. For Sourdive, the advantages of such targeted methods over recombinant techniques are robustness and reproducibility. "You know exactly what you are doing. You don't have to deal with hundreds of thousands of copies of genes that may recombine. Using targeting approaches really makes cell lines robust."

Although the science is in place—and the approval of two Shire drugs manufactured through gene-activation represents important progress—the widespread adoption of gene activation approaches in the manufacture of protein drugs is still likely to take a while, not least because of the length of clinical development. "The time to change is always long, especially when cells are being deployed. But the evolution has begun," Sourdive says.

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