when it's done to the worst case, the most extreme set of operating conditions you might run across."

Genentech achieves this by using a scale-down fermentation and recovery system. "This is in principle a wonderful concept," explains Lubiniecki, "but it requires that the manufacturer be able to document that the scale-down systems will perform identically to the full systems in terms of the principal criteria." The scale-down system has several advantages, he adds. For one, it's a great guide for development. It also allows experimentation with hazardous substances—such as radioactive materials or viruses—that would not only be undesirable in the production area, but may be expressly forbidden. One more good reason for scale-down: it would be expensive to validate at full scale because the product can't be sold.

The fifth step, product testing, follows process validation. These tests should be rigorously run on each and every product lot to reconfirm purity, safety, potency, identity, and stability. Once the product has been licensed, explains Devine, each lot released for sale will have to be cleared by FDA's division of product quality control.

The sixth and final step necessary to assure product quality is compliance with Good Manufacturing Practices (GMPs). In fact, says Devine, "we determine compliance to FDA regulations in terms of GMP requirements." FDA expects Investigational New Drug (IND)-based products to be made "as much as possible" under GMP conditions. "If you are in a pilot plant, that may not always be 100-percent-achievable, but you must at least assure us you are supplying sterile product, one that has passed the general safety test and pyrogen test. Just because an operation is small doesn't mean it can't meet GMP requirements. It doesn't have to be large: it only has to be good."

The purpose of the GMPs is to improve the quality of a manufactured product—a quality standard FDA is bound to uphold. "FDA does not get paid for approving products," says Mackler. "They get paid for keeping products that have potential health risks off the market." As rigorous as FDA's validation requirements may be, they are still only a minimum standard, claims Mackler. He urges that biotech companies strive to establish industry standards above and beyond what FDA requires. "It's not the FDA you have to worry about. A company's biggest concern is product liability. That's what will kill you."

—Jennifer Van Brunt

COMMENTARY

WHERE IS THE VIRUS? AND WHERE IS THE PRESS?

Based on evidence for antigenemia, several recent papers have suggested that the human immunodeficiency virus (HIV) may, after all, be active during the fatal, late stages of AIDS (Paul et al. *Journal of Medical Virology* **22:**357–363, 1987; de Wolf et al., *British Medical Journal* **295:**569–572, 1987; Pedersen et al., *Ibid.* 567–569; Goudsmit et al., *Journal of Infectious Diseases* **155:**558–560, 1987). If correct, these claims would lay to rest one of the nagging criticisms regarding the etiological role of HIV in AIDS—how can the virus cause such a devastating disease while remaining almost indetectably inactive?

Quantitative data in these papers indicate that at least 50 picograms (pg), and in some case up to 10 times more, viral core protein can be detected per ml of serum from AIDS patients. Their tests use a solid-phase antibody to bind HIV p24 protein, and a secondary antibody coupled to an enzyme whose activity can be measured colorimetrically. However, a simple calculation shows that 50 pg of virus core protein corresponds to about 10^5 virus particles, since a retrovirus weighs about 10^{-3} pg and roughly half its weight is core protein (Vogt, *Advances in Virus Research* **11:**293–383, 1965). If all this protein came from virions, then these patients should have titers of at least 10^5 per ml and should therefore be quite viremic.

Yet these titers of virus or even viral proteins are hard to reconcile with the extremely low level of virus expression that has been detected in AIDS patients. Typically such titers are observed in the media of confluent monolayers of fully infected cells *in vitro*, or in the sera of viremic animals. They are *not* detected in sera in which less than 1 in 10,000 target cells makes viral RNA (Ranki et al., *Lancet* **ii:**589–593, Sept. 12, 1987). Indeed, one of the papers that reports antigenemia also reports that *no* virus could be isolated from 31 antigenemic patients, even upon extended cultivation of 5×10^6 lymphocytes *in vitro* away from the virus-neutralizing antibodies of the host (Paul et al., *op. cit.*).

Why are such discrepancies not addressed in any of these papers? And this raises another question: How can we expect the popular press to achieve respectable standards in reporting AIDS-related science when scientists do not always apply the highest critical standards in journals?

Recently, reports of expression of a soluble CD4 receptor made headline news throughout the world. Yet nowhere in its own front-page article did so distinguished a newspaper as the *New York Times* raise even one of the fundamental pharmacologic questions associated with such a receptor-based therapy.

What is the half-life of the CD4 receptor on the surface of T lymphocytes? If it is long, how far does cleavage of the molecule predispose it to a short serum half-life? What is the dissociation constant of the receptor-HIV complex? What kinds of serum levels would be needed to overcome these potential biochemical constraints? Even if they could be achieved, what are the reasons to think binding of the receptor would promote virus clearance from the blood? What is the likelihood that a circulating CD4 would interfere with normal antigen processing, or interact in unpredictable ways with cellular antigens?

These issues are not trivial, and should at least serve to remind us that very little is dogma when it comes to AIDS. It is, after all, the responsibility of *both* scientists and journalists to look at data critically and ask the hard questions.

—Harvey Bialy