REGULATION

FDA LOOSENS RESTRAINTS ON CELL SUBSTRATES

BETHESDA, Maryland—The U.S. Food and Drug Administration (FDA) has issued new guidelines that should smooth the regulatory process for biologicals produced by continuous cell lines. Emphasizing that its *Points to Consider in the Characterization of Cell Lines Used to Produce Biologicals* are subject to change as new information becomes available, FDA has broadened considerably the categories of cell substrates that may be used to produce human and veterinary therapeutic products. If FDA adopts additonal recommendations drafted at a recent workshop on the guidelines, it will consider virtually any cell line as a potential substrate.

When mammalian cell substrates were first used to produce vaccines over 30 years ago, FDA mandated that the cells be derived from normal tissue. In practice, this meant that only primary cell cultures were acceptable. Eventually, FDA revised the guidelines to allow vaccine production in human diploid cell lines. More recently, an ad hoc committee advised FDA that karyological control may not be critical for cells producing substances that will be purified extensively.

Acting on this advice, FDA has drafted guidelines that deal specifically with the handling and monitoring of continuous cell lines (CCL) for production of biologicals. Several products derived from "abnormal" cell substrates—mainly therapeutic monoclonal antibodies and lymphokines—are now in the Investigational New Drug pipeline.

"There will be no total safety consideration that we can meet," Joseph Pagano (University of North Carolina School of Medicine, Chapel Hill) said at the recent FDA-sponsored workshop on the guidelines. "What we can do is reduce the unknown area to measurable parameters."

The FDA uses risk-versus-benefit criteria to evaluate new production methods, and the current policy is to review cell lines on a case-by-case basis. The clinical importance of some products that can be produced only by tumor cells has even opened the door for production of biologicals by tumor cells.

Despite the potential safety pitfalls of using CCL to manufacture biologics (not to mention public acceptance of the product) many companies have committed themselves to large scale mammalian cell production systems. They claim the advantages—larger scale, higher yield, simpler purification, better reproducibility—far outweigh the difficulties. In some cases, CCL may be the only economic way to produce a substance.

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Flow diagram for determining the acceptability of a continuous cell line (CCL) for production of vaccines. CCL producing other biologicals will receive similar scrutiny. (Redrawn from Petricciani et al. 1982. Devel. Biol. Standards *50*:15–25.)

Although the *Points to Consider* cover many technical procedures, the workshop focused on those small amounts of cell DNA or viruses that may contaminate biologically produced pharmaceutical products. These risks are not unique to CCL; any mammalian cells may harbor dangerous viruses or bits of DNA that can transform a cell and make it go amok. But unlike traditional cell culture-produced biologicals (mainly vaccines) many of the new products (interferons, plasminogen activators, blood factors) will be given in large cumulative doses to individuals in poor health. The margin of safety must be especially wide for such drugs.

Improvements in the technology for detecting DNA and viruses, however, give regulators reasonable confidence that this safety margin can be achieved. DNA probe assays detect DNA in the picogram concentration range, one-millionth the amount required to infect or transform cells *in vivo*. "We do have one limitation," warns Geoffrey Wahl (Salk Institute, San Diego, CA). "We can only specifically detect what we have a probe for. But we can determine the *level* of adventitious DNA in a sample using these assays."

As the range of acceptable cell substrates widens, the onus for ensuring safety falls increasingly on the downstream processing and purification of delicate biological molecules. Fortunately, the technology is developing to meet these demands: researchers now routinely report 10^6-fold purification, which almost invariably gives a product that meets or exceeds the current <10 picogram/dose standard. Another important element for minimizing risk from adventitous agents is process validation. A sample preparation is "spiked" with an easily detectable contaminant—highly labeled DNA or an infectious virus—and removal of the contaminant is measured during each purification step.

The scientists at the workshop were sufficiently confident about their testing protocols to recommend to FDA that there be no *a priori* proscription against any specific cell line for production of biologics. The one generally agreed upon exception to this policy is cells derived from tissue of a patient with a disease of unknown origin. (This exception was based on a case in which a patient developed Creutzfeld-Jacob disease when she received a corneal transplant from an afflicted individual.) If FDA adopts the workshop recommendations—and most regulators do seem disposed to loosen the restrictions—it will clear the way for using not only CCL, but also a number of tumor cell lines to produce new pharmaceutical products. **—Tazewell Wilson**