However, some experts are wary of current plans for preserving *Bt*'s long-term effectiveness. "*Bt* resistance management rests on a lot of theory but not much on experience," says Bruce Tabashnik of the University of Hawaii (Honolulu, HI), pointing out that "magnitude of resistance can vary up to 5000-fold." He and his collaborators were among the first US researchers to detect resistance to *Bt* in field settings, specifically in Hawaii, where the insecticide has been used to control diamondback moths. Such resistance has been documented in Hawaii, Florida, and New York, as well as the Far East, including the Philippines and China.

Many farmers and crop consultants say that the development of *Bt* resistance seems "inevitable." If efforts to control it remain ineffective, the US Environmental Protection Agency (EPA, Washington, DC) can revoke licenses, using its authority to ban specific products with "adverse effects," points out EPA Assistant Administrator Lynn Goldman. But "the EPA plans to work closely with the USDA as partners," she says.

Some argue that the USDA should take a more active "leadership" role in formulating resistance management plans and policies. But USDA officials say they are refraining from "rule making" or even outlining general policies to deter the development of resistance to *Bt*. "We want to explore these complex issues and help focus public discussions," Stauber explains. His department is urging US farmers to adopt integrated pest management strategies for combating pests and deploying specific resistance management strategies when planting genetically engineered *Bt* crops. Tacit acceptance of efforts to integrate insecticide-encoding genes into an array of major crop plants means *Bt* will find much wider use than ever before. Resistance management questions will be faced again—sooner rather than later.

*Jeffrey L. Fox*

# "Nitty-gritty" FDA guidelines wanted sooner not later

Officials of the US Food and Drug Administration (FDA, Rockville, MD) have publicly promised that efforts both to simplify the regulation of well-characterized biotechnology products and to harmonize agency procedures will be completed by late summer. But while Kathryn Zoon, director of the FDA Center for Biologics Evaluation and Research (CBER) is promising generalities—"flexibility to meet the needs of the public and of industry," and improvements in overall efficiency and performance—industry wants more detailed guidelines now.

As FDA reform progresses beyond overarching principles and entered the realm of the "nitty-gritty," the differences between the agency and industry views are beginning to become apparent.

Thus, the makers of therapeutic and diagnostic products in the biotechnology industry are indeed looking forward to less onerous "preapproval" requirements for notifying the FDA of anticipated changes in manufacturing procedures for well-characterized products. But while the FDA has proposed a three-tier classification scheme for dealing with such changes, Alan Goldhammer of the Biotechnology Industry Organization (BIO, Washington, DC) says this "may not accomplish" the regulatory relief the industry is seeking. "Our preference is for a two-tier system." Industry would notify the agency of only particularly significant manufacturing process changes before they are implemented. And, instead of filing documents with the agency each time a company adjusts a manufacturing process, it would notify the agency of most of such changes only once, as part of an annual report; many other, minor changes would not be brought to the attention of CBER at all.

Goldhammer also warns that the rule changes outlined by FDA officials contain some troubling ambiguities that could lead to the agency being "swamped" with company requests seeking clarification on which process changes are minor and which are not. "This potential problem could be avoided if the FDA was to issue guidance documents without waiting for formal federal rules," he says.

Tobias Massa, senior director of technical support worldwide regulatory affairs at Schering-Plough (Madison, NJ) and a representative for the Pharmaceutical Research and Manufacturers of America (PhRMA, Washington, DC), gives this example of the problem: If a company builds a new manufacturing facility for a particular product or begins making that product in a mammalian cell line instead of in bacterial cells, the FDA may consider that "these are not trivial changes," he says. But the company may be able to show that the product remains the same despite what appear to be "big changes from a bottom-line perspective." Clarification of such issues would go a long way toward eliminating or minimizing discrepancies between practices at CBER (which deals with biologically derived drugs) and those at the Center for Drug Evaluation and Research (CDER, which handles chemically synthesized entities).

Massa and other company representatives also suggest that everyone would benefit if the agency developed a greater trust of industry as officials fashion reforms. He believes that the FDA must learn that companies are as "concerned with public health and safety" as the agency. The agency needs to "place more responsibility on industry to police itself," he says.

Many of the reform measures pending within CBER also apply to suppliers of human blood and blood-derived products. Because the collection of blood is necessarily decentralized, any reform measures that will simplify regulations and reduce requirements for filing documents are especially welcome, according to representatives of this industry segment.

*Jeffrey L. Fox*

# 2010—a pig odyssey

The 1995 Xenotransplantation Foresight Study*—about to be published in the specialist newsletter *Xeno*—concludes that it will be more than a decade before pig organs are given to human patients on a regular basis. And it will be several years into the next millennium before xenotransplanted livers and hearts first enter clinical trials.

The data for the Xenotransplantation Foresight Study was gathered from *Xeno* readership—an international and multidisciplinary population of immunologists, molecular biologists, clinicians, and other stakeholders spanning the fields of immunology, cell biology, surgery, transplantation and related disciplines. Unsurprisingly, the committed group envisages a bright future for xenotransplantation. Nonetheless, they also highlighted key issues remaining to be solved, and the consensus view is that the obstacles will not be overcome untill early next century.

The major obstacle to xenotransplantation is the activation of complement in the recipient because of the presence of preformed antibodies that recognize particular carbohydrate antigens on the graft. During the subsequent "hyperacute rejection," the transplant is rapidly and violently rejected. The problem is particularly serious for "discordant" pig-to-human grafts. Nevertheless, as the survey confirms, the pig remains the over-