*John E. Frydenlund*
*Deputy Assistant Secretary*
*Marketing and Inspection Services*
*U.S. Department of Agriculture*

# *USDA Regulation of Animal Biotechnology*

In this presentation I will share with you a U.S. Department of Agriculture (USDA) perspective on some of the regulatory issues associated with animal biotechnology. You are all aware of the Federal Coordinated Framework for biotechnology oversight that has moved products of biotechnology from the laboratory to the marketplace. Under this policy, federal agencies use their existing statutory authority to regulate the products of biotechnology.

The product reviews focus on the nature of the product and the risk, rather than the process used in its development. Federal agencies are required to ensure protection for public health and the environment from any potential harmful effects of these products. Favorable evaluations of the job the agencies are doing were published by the U.S. General Accounting Office and by the Office of Technology Assessment in 1988.

The *"Report on National Biotechnology Policy*," released by the Council on Competitiveness in the Office of the Vice President in 1991, reaffirmed the Administration's commitment to maintaining the U.S. lead in biotechnology research and product development over the long-term. The report provided an update on the Coordinated Framework and restated several principles for guiding federal regulatory policy:



—Federal oversight should focus on the characteristics and risks of the product, not the process, used in its development;
—Regulatory review should be designed to minimize burden while assuring protection of public health and welfare;
—Regulatory programs should be responsive to rapid advances in biotechnology.

The Council on Competitiveness' report also recommended publication of a document to help federal agencies make decisions, within the scope of authority afforded by statute, on how to regulate planned introductions of biotechnology products. The statement was published in February, 1992. It will ensure that federal oversight is used where it will do the most good—that is, where the risks are real.

We are using these principles to refine the management of our biotechnology programs at USDA. I would like to mention some of our management initiatives and then discuss the regulation of animal biotechnology.

USDA has both research and regulatory responsibilities for agricultural biotechnology and they are administered separately. The Assistant Secretary for Marketing and Inspection Services oversees the Department's biotechnology regulatory activities through a delegation of authority from the Secretary of Agriculture.

The counterpart for research is the Assistant Secretary for Science and Education. Together they co-chair the Committee on Biotechnology in Agriculture (CBA) which was established in 1986 as USDA's policy-making and coordinating body for biotechnology.

The members of the CBA are the administrators of all the USDA agencies that administer biotechnology programs—the Animal and Plant Health Inspection Service (APHIS), the Food Safety and Inspection Service (FSIS), Agricultural Research Service, the Cooperative State Research Service, the Economic Research Service and the Forest Service.

The CBA met recently (Spring, 1992) to review a strategy that we believe will improve the effectiveness of our biotechnology programs. Several of these initiatives are the result of a study of USDA management of critical issues, including biotechnology, that cut across the jurisdiction of individual agencies:

—We have solicited proposals for the biotechnology risk assessment research program stipulated in the 1990 Farm Bill. The purpose of the program is to strengthen the scientific basis of USDA's regulatory programs.

—We approved a public information plan on biotechnology for the Department. This is a priority program. We have been providing information for a long time on an agency-by-agency basis and the time has come to launch a Department-wide effort. We began the program this spring by co-sponsoring a joint U.S. and European Community (EC) meeting on biotechnology communication in Dublin, Ireland.



—USDA agencies are implementing the President's Biotechnology Research Initiative. This involves reporting and monitoring of the Department's $162.6 million 1992 research budget for biotechnology and reassessing our research priorities.

—We are committed to fostering trade through scientific meetings that will lead to international consensus on biosafety issues. USDA scientists are involved in the negotiations sponsored by the major international organizations including the EC and the Organization for Economic Cooperation and Development (OECD).

## REGULATING PRODUCTS OF ANIMAL BIOTECHNOLOGY

Now I will turn to the activities of the two USDA regulatory agencies directly concerned with regulating the products of animal biotechnology—APHIS and FSIS. Both agencies have authority, in the broadest sense, for protecting animal health.

*Animal and Plant Health Inspection Service (APHIS)*

The Virus-Serum-Toxin Act of 1913, as amended, gives APHIS the authority to regulate all veterinary biological products imported into the U.S. or exported, or those biologics shipped or delivered for shipment interstate or intrastate.

Veterinary biological products are defined in the regulations [9 CFR 101.2(w)] as all viruses, serums, toxins and analogous products of natural or synthetic origin intended for use in the diagnosis, treatment or prevention of diseases of animals.

The licensing requirements [9 CFR Part 102] include tests to insure purity, safety, potency and efficacy. Pre-licensure evaluation of all veterinary biological products—regardless of the techniques used in their development—is performed at the National Veterinary Services Laboratory (NVSL) in Ames, Iowa. The NVSL is the only federal facility in the U.S. engaged in the evaluation of veterinary biologies and the diagnosis of domestic and foreign animal diseases.

It was nearly ten years ago that APHIS issued the first license for a veterinary biological product developed through biotechnological techniques. Since then, 48 product licenses have been granted for three broad categories of these products. The categories are based on the biological characteristics of the product and the kinds of safety issues it presents. Category one includes inactivated recombinant DNA-derived vaccines, bacterins, bacterin-toxoids and virus or bacterial subunits.

Hybridoma-derived monoclonal antibodies as well as genetically engineered antibodies are also included in this category. These nonviable, or killed, products pose no risk to the environment and present no new safety concerns. An example of a category one product is the *Escherichia coli* bacterin used to protect swine against Colibacillosis, a disease that has severe economic effects on swine producers.



The diagnostic test kits classified as category one products represent a significant breakthrough in animal disease diagnosis and treatment. Pseudorabies diagnostic test kits which can differentiate between reactions caused by wild type viral infections and immunization with recombinant vaccines, are used in APHIS' Pseudorabies Eradication Program.

Category two products contain live microorganisms that have been modified by the addition of marker genes or the deletion of genes that code for virulence. Special precautions are taken to ensure that the addition or deletion of genetic information does not confer virulence, pathogenicity or survival advantages to these organisms that are greater than those found in the parent or wild type forms. All the licensed category two products are for use against pseudorabies in swine and involve gene deletions or additions.

Category three includes products containing live expression vectors carrying recombinant DNA-derived sequences that code for immunizing antigens

or other immune stimulants. The transmission characteristics of such products must be carefully assessed before field studies are undertaken.

While no licenses have been granted in category three, one product is currently being field tested after a thorough evaluation of safety data. The product is a live recombinant DNA-derived vaccine-vectored rabies vaccine intended for oral use in raccoons in the wild. The incidence of rabies has increased dramatically in the Mid-Atlantic States and public health officials have been enthusiastic about the potential of immunizing animals in the wild with the recombinant vaccine contained in food bait. Field tests have been conducted on Parramore Island in Virginia and in Sullivan County, Pennsylvania.

Additional tests have begun in a three-county area in New Jersey. Since December, 1989, there have been 1700 cases of rabies in New Jersey and 90 percent of the cases have been in raccoons. The disease is moving from North to South in the State and New Jersey public health authorities hope to establish a rabies-free zone by concentrating the bait drops in Cape May County. There will be extensive monitoring before and after another bait drop in Fall, 1992.

The states must approve field tests of all experimental biologies so we have worked closely with state officials to provide the public with information on the rabies vaccine field trials. APHIS scientists attended state-sponsored public meetings to answer technical and scientific questions and an APHIS spokesperson was interviewed in the Spring, 1992, on Cable News Network (CNN) about the New Jersey tests. The vaccine trials were also featured in a new publication on biotechnology distributed in March, 1992, to junior high school students throughout Pennsylvania.



Future generations of vaccines will combine the genetic information to immunize against several diseases into one virus or bacteria. We have now received an application for a genetically engineered category three vaccine with antigens against two disease agents in the same microorganism. This will improve the consistency of production from lot to lot of product, by eliminating variation in antigen content when different components are mixed together.

For the category two licenses and the field trials of the category three rabies vaccine, APHIS prepared a complete environmental assessment of the proposed action in compliance with the provisions of the National Environmental Policy Act. The environmental assessments provide the public with a discussion of scientific data on safety and a thorough analysis of environmental impacts.

When any project has implications for public health, expert panels consisting of representatives from federal agencies, academic institutions and professional societies are convened to review data. Additional review can also be requested from the National Vaccine Program in the Department of Health and Human Services which was done for the rabies vaccine.

Early generations of veterinary biological products developed through biotechnology have proved effective in disease prevention and diagnosis. Succeeding generations will be even more effective and we look increasingly to global markets for these products.

The growth of international ownership of the biologics production industry and the advent of the European Community (EC) have increased the immediacy of the drive for internationally recognized standards and consistency in testing procedures. We have worked with a number of international groups to further this process. In one of these efforts, U.S. and EC representatives met in France in January, 1992, to work toward the standardization of production practices. The discussions continued during that summer.

There is pressure on the U.S. to increase the potential for EC-produced biologics to enter U.S. markets. Many of these products are prevented entry because of the presence of foot and mouth disease and bovine spongiform encephalopathy in several EC countries. We are working to resolve these and a number of other issues.

*Food Safety and Inspection Service (FSIS)*

Turning now to the role of the Food Safety and Inspection Service in regulating animal biotechnology, this will be brief because Dr. Cross has already done such an able job on this subject (see page 121). The summary statement from last year's NABC workshop on transgenic animals is a good place to begin and I quote:

> In general, workshop participants concluded that public issues associated with transgenics were not urgent, primarily because applications of transgenic technologies as they affect agriculture and the food supply seem remote at the present time. (Murray et al., 1991, p. 43)



We think that if we do our work well enough, public issues associated with transgenics will *not* become urgent. This means that we must continue to maintain an open dialogue on potential issues before they develop. We talk to our critics, as well as to the regulated public, and we join with other federal agencies in sponsoring workshops and discussion groups.

These statutes from which FSIS gets its authority for regulating the animal products of classical breeding and new technologies are the Federal Meat Inspection Act and the Poultry Products Inspection Act.

These statutes require that FSIS inspect cattle, sheep, swine, goats, equine, poultry and food products prepared from them intended for use in human food to assure that they are wholesome, not adulterated and properly labeled, marked and packaged. The FSIS policy statement in the 1986Coordinated Framework established the applicability of the experimental animal regulations for the use of genetic engineering techniques in food animals [9CFR309.17and381.75].

This policy was reaffirmed in a *Federal Register* notice published in December, 1991. The notice pointed out that only a small proportion of the animals in gene transfer experiments contain the intended gene [56 FR 67054-67055]. Before animals that do not contain the experimental transgene may be presented for slaughter, data must be submitted to FSIS demonstrating that the transgene is not present and that the animals are therefore "not adulterated." Written approval for slaughter of an animal determined to be nontransgenic is granted by the FSIS Deputy Administrator for Inspection Operations and the animals are subject to the same inspection procedures as conventionally bred animals. Animals have been approved for slaughter under these provisions. We expect a number of applications to be considered in the near future. We know that the cost of maintaining these animals is prohibitively high.

A document is being prepared which pertains to the food safety evaluation of transgenic animals being considered for slaughter. In making an evaluation, FSIS may consult with other agencies, including the Food and Drug Administration (FDA), the Environmental Protection Agency (EPA) and APHIS. Interaction among federal agencies to consider these issues has been taking place for several years through the meetings of the Food Animal Biotechnology Information Exchange Group. Through these discussions we are working to anticipate both scientific and consumer issues, and to avoid delays due to agency concerns about jurisdiction.

We know that research using molecular methods will bring revolutionary advances in animal science. The realization of much of this promise is in the future for the development of animals bred for special qualities such as disease resistance. However, this research has already brought us quantum increases in our knowledge of gene function. There have been many notable breakthroughs. Transgenic animals have proven very useful as models for the development and treatment of a variety of human diseases. The use of large animals as bioreactors has resulted in the development of sheep that secrete such substances as Clotting Factor 9 in their milk, and transgenic pigs that carry quantities of human hemoglobin in their blood.



There are any number of applications of biotechnology to animal science and production agriculture that are scientifically successful including the production and use of bovine and porcine growth hormones. One application, in particular, must be singled out because it relates directly to the FSIS responsibilities for food safety. The availability of DNA probes to test for the presence of bacterial pathogens in meat and meat products has cut the detection time by one-half. These molecular methods are also highly sensitive and cost-effective.

The use of existing statutes and procedures to evaluate the products of animal biotechnology has allowed us to anticipate the testing and marketing of new products. We have ensured our capability for dealing with the new techniques by hiring specialists and through training programs for our staff

scientists. We urge researchers to meet with us to discuss any questions they may have about regulations for testing and product development.

## CONCLUSION

In closing, I would like to emphasize the point Dr. Cross made about the importance of consumer interests and perceptions (see page 125). USDA agencies, including FSIS and APHIS, work closely with consumer-interest groups to inform the public about our oversight policies and programs for biotechnology products and to discuss any safety concerns associated with production and marketing.

The potential of biotechnology for improving animal health and the quality of meat and meat products is immense. We believe that risk-based regulatory programs will help realize the benefits of the technology for both U.S. consumers and producers.

## REFERENCES

Murray, J., P.B. Thompson and R. Piggott. 1991. Transgenic Animals. In *NABC Report 3, Agricultural Biotechnology at the Crossroads: Biological, Social and Institutional Concerns.* J. Fessenden MacDonald, ed. National Agricultural Biotechnology Council. Ithaca, NY p. 43.