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REGULATORY ISSUES IN AGRICULTURAL BIOTECHNOLOGY

This information was presented at the Conference on Urban/Rural Environmental, Food, and Agricultural Issues: Problems and Solutions for the Next Generation at California State Polytechnic University, Pomona, California, on November 14, 1997. Remarks were prepared by G.A. Mitchell, D.V.M., C. Haley, Ph.D., M. Miller, Ph.D., J. Matheson, and W.D. Price, Ph.D.

Under the provisions of the Federal Food, Drug, and Cosmetic Act (FFDCA), in part, the Secretary of HHS promotes honesty and fair dealing in the interest of consumers through regulations that establish specifications and quality standards for food intended for man or animal. Food is considered adulterated, in part, if it bears or contains any poisonous or deleterious substance which may render it injurious to the health of man, animals, or the environment. A food is also misbranded if its labeling is false or misleading in any particular, for example, if it is offered for sale under the name of another food.

The genetic modification of food-producing animals to produce a human biologic (e.g., vaccine) or human or animal drug; or to optimize the nutritional value of derived food products; or to increase growth rate, reproduction, or resistance to disease can fall under the provisions of the FFDCA.

Biological products for administration to animals are regulated under the Virus, Serum, Toxins Act (VSTA). This act was recently amended and the final regulations

implementing the amendments were published in the June 9, 1997 *Federal Register* (62 FR 31326).

The Environmental Protection Agency regulates pesticides used in or on food or feed under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and the FFDCA and controls the use of certain genetically engineered microorganisms under the Toxic Substances Control Act (TSCA).

The environmental safety of the field testing of most genetically engineered plants is regulated by the Animal and Plant Health Inspection Service (APHIS) under the authority of the Federal Plant Pest Act and the Plant Quarantine Act.

The USDA Food Safety and Inspection Service (FSIS) is responsible for ensuring the safety, wholesomeness, and accurate labeling of meat, meat food products, and poultry products under the Federal Meat Inspection Act and Poultry Products Inspection Act.

The FDA regulates drugs for use in animals. The FFDCA defines "drugs" to include, among other things, articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of diseases in man or other animals; and articles (other than food) intended to affect the structure or any function of the body of man or other animals. Articles that are used to improve animal performance, such as increased rate of gain and improved feed efficiency, are "drugs" under the FFDCA. Section 902(c) of the FFDCA states that nothing in the FFDCA shall affect, modify, repeal, or supersede the provisions of the VSTA. FDA regulations under 21 U.S.C. 510.4 provide that an animal drug produced in full conformance with the VSTA will not be subject to the new animal drug approval requirements of the FFDCA.

Under the VSTA, the term "biological products," also refers to biologics, biologicals, or products, and shall mean all viruses, serums, toxins (excluding substances that are selectively toxic to microorganisms, e.g., antibiotics), or analogous products at any stage of production, shipment, distribution, or sale, which are intended for use in the treatment of animals and which act primarily through the direct stimulation, supplementation, enhancement, or modulation of the immune system or immune response. The term "biological products" includes, but is not limited to vaccines, bacterins, allergens, antibodies, antitoxins, toxoids, immunostimulants, certain cytokines, antigenic or immunizing components of live organisms, and diagnostic components, that are of natural or synthetic origin, or that are derived from synthesizing or altering various substances or components of substances such as microorganisms, genes or genetic sequences, carbohydrates, proteins, antigens, allergens, or antibodies.

Analogous products shall include:

(i) Substances, at any stage of production, shipment, distribution, or sale which are intended for use in the treatment of animals and which are similar in function to biological products in that they act, or are intended to act, through the stimulation,

supplementation, enhancement, or modulation of the immune system or immune response; or

(ii) Substances, at any stage of production, shipment, distribution, or sale, which are intended for use in the treatment of animals through the detection or measurement of antigens, antibodies, nucleic acids, or immunity; or

(iii) Substances, at any stage of production, shipment, distribution, or sale which resemble or are represented as biological products intended for use in the treatment of animals through appearance, packaging, labeling, claims (either oral or written), representations, or through any other means.

The term "treatment" shall mean the prevention, diagnosis, management, or cure of diseases of animals.

It is now recognized in the scientific literature that the generation of stimulation of an immune response involves both antigens and certain protein regulatory factors referred to as cytokines. Some cytokines (e.g., interleukins) serve as essential components in the generation and expression of an immune response, without which the vaccine would be worthless. These cytokines may be elicited through stimulation with antigens or certain "immunomodulators". Cytokines are also produced in many body tissues and act on cell types other than those of the immune system. Cytokines of natural or synthetic origin can be prepared as products for administration to animals. Because of the diverse biological activity of the cytokines, not all products consisting of these substances would be regulated under the VSTA. Many of these cytokines intended to be used as drugs would fall under the jurisdiction of the Food and Drug Administration. In such instances, the VSTA would not apply.

Both cytokines and immunomodulators are analogous to biological products when they are used to stimulate, supplement, enhance, or modulate the immunity of animals in the treatment of disease. Products consisting of these substances that work through these immune mechanisms in the treatment of specific disease appropriately fall within the definition of "biological products".

In summary, when a cytokine modulates or stimulates an immune response in a way that is similar to that of a vaccine, bacterin, allergin, antibody, antitoxin, toxoid as outlined in the definition of a biological product the cytokine product will be regulated under VSTA. In the event that the natural or synthetic cytokine has activity which would extend beyond a single disease organism, the product would be regulated under the FFDCA.

FDA is the primary agency responsible for the regulation of food products intended for human consumption, except for meat and poultry. FDA has responsibility for the safety of milk and dairy products, fish and shellfish and animal drug products. To date, FDA has not published a formal policy statement on how the FFDCA applies to the regulation of new gene transfer technologies when applied to food-producing animals.

The FFDCCA defines drugs, as described above, based upon their functional claims rather than their chemical structure or manufacturing source and thus, some transgenic animals will be regulated, in certain respects as a drug, under the animal drug provisions of the FFDCCA. Most of the transgenic animal experiments conducted to date involve the introduction of the genetic material into the germ line or somatic cells. When the genetic material is introduced into somatic or germ cells to produce phenotypic change that meets the definition of a drug in the animal or its offspring, the expressed drug product would be considered to be a new animal drug. On the other hand, when a genetic procedure is used to map the genome, and phenotypic change is achieved through traditional breeding, it would not be considered to be a new animal drug.

The following material is taken from "Food Safety Evaluation of Transgenic Animals," in Transgenic Animals Generation and Use, edited by Louis Marie Houdebine:

"To date, the biotechnology products approved by CVM have been proteins produced by recombinant DNA technology using a bacterial fermentation system. The desired gene is isolated and fused with plasmid DNA. The recombinant plasmid is cloned or inserted into a gram negative bacterial host, usually *Escherichia coli*. Under fermentation conditions, these transformed microorganisms become factories which produce large quantities of the protein hormone at relatively low cost. The protein product is isolated and purified from the bacteria. When treated under defined conditions, the product assumes a conformation which is biologically active. In many respects, the production of recombinant protein hormones is not substantially different from the production of other new animal drugs made by the more traditional fermentation processes.

The food safety evaluation for recombinant protein hormones is similar to that performed for other protein products approved as animal drugs. On the other hand, the toxicology studies conducted to demonstrate the human food safety of protein products are considerably different from drug products. With the consent of the drug's sponsors, CVM has published a comprehensive review of the food safety evaluation for bovine somatotropin describing the studies required for this recombinant protein hormone product (Guyer and Juskevich, 1990).

The statutory food safety requirements for animal drug residues in genetically modified animals are the same as those for other animal drugs. Basically, the food products produced from genetically modified animals must be as safe as those from nontransgenic animals; and the sponsor of the transgenic animals must demonstrate safety of the animal products before the animal can enter the food supply. The standard battery of toxicology studies used to establish the safety of "traditional" animal drugs are not appropriate for assessing the safety of a transgene in genetically modified animals. Also, the "traditional" withdrawal period may not apply to transgenic animals. Although it may be possible to "turn-off" the expression of the transgene, and thereby limit exposure to the expression product; it will not eliminate the transgene from the animal. In cases where there are food safety concerns for the expression products and not the transgene, a tolerance approach could apply.

Biopharm animals have been genetically modified to manufacture a human or veterinary drug, biologic, a food additive, or other product of commercial value. The substance is then harvested from milk, blood or other tissue of the biopharm animal. The genetic modification can be a germ line, heritable modification, or a somatic cell or gene therapy involving the introduction of the modified genes into cells of a particular tissue of an individual. The main emphasis of these efforts is on harnessing the metabolic capabilities of the animal to produce a product in lieu of using, for example, chemical synthesis, fermentation, or extraction from a dilute natural source.

Transgenic animals may also be modified to include food or color additives intended to affect the quality of animal-derived human food. Examples might include cattle that produce more nutritionally complete milk, fish that produce more omega-3 fatty acids, or trout with pink muscle tissue.

In summary, many of the product claims being anticipated for transgenic animals, for example, improved growth, improved feed efficacy, improved carcass characteristics, and improved disease resistance, are the same as animal drug claims. Any regulation of transgenic animals under the FFDCa will require demonstration of human food safety. The food safety evaluation under the animal drug provisions of the FFDCa is science-based and its inherent flexibility can accommodate the additional products and animals carrying or sold with animal drug claims."

In respect to genetically engineered plants, on June 26, 1986, FDA published a coordinated framework for the regulation of biotechnology in the *Federal Register* (FR). It stated the intention by FDA to regulate foods and feeds that are produced by rDNA technology under existing laws and regulations. The FR indicated that, in some instances, whole food derived from a new plant variety including a food from a genetically modified plant might fall within the scope of a food additive. FDA received comments requesting clarification of the regulatory status of foods such as, fruits, vegetables, grains, and byproducts from plants developed by use of rDNA technology.

FDA reviewed the comments and published the FR Notice entitled "Statement of Policy: Food Derived from New Plant Varieties" on May 29, 1992. This statement laid out the issues that individuals should consider during the development of new plant varieties including those using rDNA techniques. FDA noted in its response that the safety of a food is regulated primarily under its post-market authority in Section 402(a)(1) of the FFDCa. It also stated that it is the transferred genetic material and the expression product that might be subject to the food additive regulations, if they are not generally recognized as safe (GRAS). It further stated that the Notice was being published to ensure that the relevant scientific, safety, and regulatory issues are resolved prior to the commercial sale of the products.

After the publication of the policy, the Center for Food Safety and Applied Nutrition (CFSAN) and the Center for Veterinary Medicine (CVM) developed a document to outline the consultation process for a developer of a new plant variety to follow in consulting with the Agency about the safety and regulatory issues prior to the marketing

of the new product. Typically, the developer initiates dialog with FDA and then can submit summary information about the safety and nutritional assessment of each plant transformation event. The Agency may then conclude the consultation process by issuing a letter to the developer which indicates that there are no unresolved issues associated with that variety (event). The consultation procedures are described in detail on CFSAN's WWW site (<http://vm.cfsan.fda.gov/~lrd/consulpr.html>). Please make reference to that site for specific details.

The use of antibiotic resistance marker genes in the development of biotech plants has been a concern. Plant breeders have indicated in the consultation process with FDA that kanamycin (kanr), lactam, chloramphenicol and amino glycoside antibiotics have been used in the development of modified plant varieties. To date, only the Kanr expression product, amino glycoside 3'-phosphotransferase II (NPT), has been shown to be expressed in modified plant varieties. A food additive regulation was established to allow the use of NPT II in canola, cotton, and tomatoes. In other cases the gene coding for antibiotic resistance is present in the plant, but the expression product is not, because the gene does not have the right regulatory sequences for expression in the plant. The known mechanisms for gene transfer lead us to believe that it is highly unlikely that a functional copy of these genes would be transferred from the plant to rumen, environmental, or gut microflora.

A list of plant varieties which have completed the consultation process is maintained at the CFSAN WWW site (<http://vm.cfsan.fda.gov/~lrd/biocon.html>).

The FDA role is to assure the safety of the products it regulates.