

CASE STUDY No. IV

FARM ANIMAL (GOAT) THAT PRODUCES HUMAN DRUGS

Overview

This case study examines in a general way the proposed use of genetically engineered animals to produce protein biologics for use in human therapy, referred to herein as “human biologics¹,” “human proteins,” or “transgenic proteins,” including the disposition of those animals. The case study uses the example of a goat engineered to express a human protein in its milk. The protein is then extracted and purified for therapeutic use in humans. While there are products under review, because no such product has completed the Food and Drug Administration (FDA) regulatory process, this case study is relatively general.

1. Description of proposed organism/product and its use

Genetically engineered (transgenic) farm animals are currently being developed through the use of recombinant DNA methods for production of therapeutic proteins for human medical uses. For example, exogenous DNA encoding a human protein may be inserted into an animal genome in such a way as to allow the expression of the heterologous protein in the milk of the transgenic animal. Once secreted into the milk, these recombinant proteins can be efficiently purified from milk and manufactured into biological products that are used therapeutically to treat disease in human beings. Transgenic animals modified to produce proteins for extraction, purification, and therapeutic use are referred to in this case study as “biopharm animals”.

Production of medically useful human proteins in the milk of biopharm animals has the potential for providing an efficient and convenient method for generating large quantities of biologically active proteins and for thereby reducing the cost of pharmaceutical manufacturing. Currently, several blood clotting factors and enzymes for replacement therapy in metabolic diseases are being manufactured using this technology and are in early stages of development and testing. It is anticipated that other biological products, including therapeutic, blood and vaccine products for human use will be considered for production in biopharm animals. Several species of animals including goats, sheep, cows and rabbits are being developed for transgenic production of biologically active proteins. Research and development of this technology is currently being performed at specialized research farms and facilities in several sites in the U.S. and Europe.

¹ The term “human biologic” refers to a biologic intended for treating people. Human biologics generally are derived from biological sources and include substances such as blood, vaccines, and biologically active proteins. The term “human protein” is used in this case study to refer to a protein produced in humans, or the same protein produced in an animal through genetic engineering. The term “transgenic protein” refers to a protein produced from a gene introduced into the animal by genetic engineering. In this case study, the terms are used interchangeably, because the transgenic protein to be used as a biologic is a human protein.

Biopharm animals are initially generated in the laboratory by introducing well-characterized, sequenced recombinant DNA either into gametes (i.e., a mature reproductive cell --haploid set of chromosomes-- capable of fusing with a similar cell of opposite sex to yield a zygote) or early embryonic stages. Once the DNA is stably integrated into the animal genome, it can be transmitted to subsequent generations through breeding. The genetic construct is engineered so that the transgenic DNA is present in all cells in the animal but the encoded protein is expressed at high levels only in the milk.

Transgenic animal production of biologics begins with the generation and maintenance of animals producing recombinant proteins in the milk. This occurs on specialized dairy farms that are well-controlled facilities that provide both animal husbandry and milk collection services. These dairy facilities are designed to utilize state-of-the-art milking practices and equipment for single-product-dedicated milking. Milk containing the human protein is collected from lactating animals, pooled after initial testing and then frozen. The frozen milk is shipped to other manufacturing facilities where the human protein/biologic is extracted, purified and characterized. The final product is further tested and formulated for clinical use. Because of the yield advantage of biopharm production, it is anticipated that in most cases, at least for the kinds of products currently under development, relatively small farms with small herds could produce sufficient amounts of product to satisfy all medical need.

Companies have strong economic incentives to ensure that their animals, which are very expensive to develop, do not escape and interbreed with other animal stock. Biopharm animals producing milk are held in dedicated and separated pens and paddocks enclosed in areas with double fence-lines to facilitate isolation of animals from contact with other livestock, predators and pests, and to prevent escape of the animals. General management practices for these specialized farms include: relative isolation from other livestock on land without a history of infectious disease affecting livestock; use of breeding stock that are free of infectious disease; construction of high quality facilities that serve as a barrier to disease introduction from local feral and domestic livestock; maintenance of high standards of animal husbandry and veterinary care; careful monitoring of the health of animals and personnel; disease prevention programs; tracking of all animals and farm resources; and adhering strictly to written standard operating procedures (SOPs). In addition, the facilities are designed to prohibit entry by unauthorized personnel or equipment.

Disposal of ex-producer animals may require specialized facilities for burial or cremation. Environmental issues posed by burial or cremation would in general be associated with the amount of biomass of animal to be disposed of, rather than specific to the fact that the animals were transgenic. As discussed in Section 2 below, should developers propose to dispose of research animals or ex-producer animals by slaughtering or rendering them for food or feed, they would need prior approval from FDA, and to get such approval would have to demonstrate to FDA that meat from such animals would be safe for food or feed. In addition, developers would need Food Safety Inspection Service (FSIS) approval for slaughter of the animals for food. FDA is

considering developing draft guidance to address various issues pertaining to FDA regulation of transgenic animals, including the kinds of information necessary to get approval for food or feed use. This draft guidance will have formal public input before becoming final. FDA and FSIS also intend to engage in public discussion on public policy issues pertaining to the potential disposal of biopharm animals through slaughter or rendering for food or animal feed use.

Sanitary waste generated from farms growing biopharm animals is handled the same way as waste generated from any animal production facility in which animal drugs are used. Farms housing biopharm animals follow federal, state, community and Tribal rules pertaining to agricultural waste. Waste is directed to local septic tanks and subsurface septic fields and is not released into public sewage.

Advantages of transgenic animal production of human pharmaceuticals

The use of transgenic animals to produce therapeutic proteins can have potential economic advantages that also provide indirect benefits to the environment, such as reduced energy and other manufacturing inputs, as compared to traditional protein production methods that use large scale bioreactors in conventional large-scale production plant facilities.

Transgenic animal production of therapeutic proteins offers several potential technical advantages compared to production in bacteria such as *E. coli*, in fungi, and in cell tissue culture. Production in *E. coli* is very efficient but limited to simple, non-glycosylated proteins, which makes this approach unusable for many human biologics. Although the cost of production in *E. coli* is low, the usefulness of the final protein product may be limited due to the lack of proper folding and post-translational processing.

Systems that use fungi such as yeast or filamentous fungi are efficient in production of some secreted proteins, but glycosylation patterns are non-mammalian. Non-mammalian glycosylation can reduce the efficacy of the resulting biologic by affecting the pharmacokinetics and immunogenicity of the protein. In general, proteins produced in transgenic animals are usually complete and have the same, or very similar, folding and processing characteristics as native protein.

Cell tissue culture provides the standard method for producing complex glycosylated proteins that are properly folded with useful post-translational processing. However, low yields and associated high cost of production are limiting factors for the number of proteins that can be developed. Because of the high yield of protein per animal, transgenic animals potentially can provide a cost-competitive means for large-scale production of therapeutic complex proteins. Several factors, including high milk yield, high recombinant protein content, short gestation period and short time-to-maturation make goats particularly well suited for biopharmaceutical development and scale-up for commercial production.

2. Relevant regulatory agencies, regulatory authority and legal measures

Transgenic animals that produce human biologics are regulated under both the Public Health Service Act (PHS Act) and the Federal Food, Drug, and Cosmetic Act (FFDCA). As discussed below, such animals contain both a new² animal drug and a human biologic, and in most cases would be regulated by both the Center for Veterinary Medicine (CVM) and Center for Biologics Evaluation and Research (CBER) of FDA. Sponsors are also subject to Environmental Protection Agency (EPA), state, local and tribal requirements regarding disposal of wastes. In addition, under FSIS regulations, livestock and poultry used for research must receive FSIS approval prior to slaughter for human food.

The agency intends to issue draft guidance to address various issues pertaining to FDA regulation of transgenic animals. It is currently envisioned that the first of these documents will explain how the PHS Act and FFDCA apply to transgenic animals, help developers understand their obligations under the relevant provisions of those laws, and clarify the respective roles of CVM and CBER in regulating the animal drug and human biologic components of transgenic animals. Other guidances will be developed as the technology matures. Scientific and open public meetings on the use of transgenic animals to produce pharmaceuticals may also provide subjects for further guidance documents.

The PHS Act states that a biological product "means a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product . . . applicable to the . . . treatment of a disease or condition of human beings." 42 USC 262(i). Thus, the transgenic protein extracted from a biopharm animal and intended to be used for the "treatment of a disease or condition of human beings" would be regulated as a biological product under the PHS Act. It also would meet the definition of a drug, as would the gene encoding the transgenic protein.

The FFDCA defines a "drug" to include "articles . . . intended to affect the structure or any function of the body of man or other animals." 21 USC 321(g). Because an introduced genetic construct encoding a human biologic would of necessity "affect the structure or . . . function" of a biopharm animal, the genetic construct meets the definition of a "drug." Because in general the genetic construct would not be "generally recognized . . . as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof," it would meet the definition of a "new animal drug." 21 USC 321(v). This means that the gene construct in the biopharm animal is both a new animal drug and part of the process for the production of a human biologic. FDA, therefore, has the authority to regulate a transgenic animal engineered to produce a human biologic under two distinct but complementary regulatory schemes.

² ("New" with reference to animal drugs is a statutory term (21 U.S.C. 321(v)) that applies essentially to all animal drugs.)

Under the FFDCA new animal drug approval scheme, use of a new animal drug is considered "unsafe" unless the FDA has approved an application for that particular use. 21 USC 360b. A sponsor can conduct research on an unapproved new animal drug under an exemption for an investigational new animal drug (INAD). 21 U.S.C. 360b(j). 21 CFR 511.1. A sponsor can conduct new animal drug research without an INAD as long as the animals are used solely for laboratory research, and also not to be used for any food or feed purpose. The sponsor conducts research on the biopharm animal while the INAD is in effect. When completed, the research can become the basis of a new animal drug application (NADA). 21 U.S.C. 360b(b)(1).

FDA evaluates the NADA to determine whether the sponsor has demonstrated that the new animal drug is safe and effective for its intended use. The burden of proving that the drug meets this standard is entirely on the sponsor. The determination of whether a new animal drug is "safe" includes an evaluation of the new animal drug's environmental effects on the health of humans and animals. For new animal drugs intended to be used in food animals, FDA has to determine whether food products (e.g., meat, milk, eggs) from animals treated with the new animal drug are safe for human consumption. While the INAD is in effect, were a sponsor to propose to slaughter or render a transgenic animal for human food or animal feed, the sponsor would first have to obtain FDA authorization to do so. 21 CFR 511.1(b)(5). FDA would inform FSIS of its decision. Under 9 CFR 309.17 and 381.75, a sponsor would also have to get FSIS authorization to slaughter a transgenic research animal for human food.

Under the PHS Act, in order for a manufacturer to ship a biological product in interstate commerce, the manufacturer needs an approved Biologics License Application (BLA) for that product. 42 USC 262(a)(1). FDA will approve a BLA on the basis of a demonstration that the product is safe, pure, and potent and that the facility and animals in which it is manufactured meets standards designed to ensure its continued safety, purity, and potency. 42 USC 262(a)(2)(B). For a human biologic, the "safety" determination includes an evaluation of the biologic's potential environmental effects on human health.

FDA usually begins to regulate a human biological product under the FFDCA at the time that the sponsor is preparing to initiate human clinical trials of the product. This regulation includes licensure under the PHS Act and continues through the monitoring of post-marketing compliance with applicable requirements. Initially, the sponsor will either submit an Investigational New Drug application (IND) or request a pre-IND meeting to discuss the product and its clinical development. To initiate a clinical study, a sponsor must have an IND in effect. 21 USC 355(i); 21 CFR Part 312. The IND regulations are designed to protect human subjects in clinical trials and thus set forth requirements for sponsors and investigators concerning, among other things, reporting, record keeping and informed consent.

At the IND stage, considerable information about the product and its mode of manufacture are required to assess its suitability for clinical trials. Much of this data, including specific information about the transgene, its stability, the animal husbandry

used to maintain the animals and their ultimate disposition are useful in determining whether a potential for an adverse environmental impact exists.

Because FDA will evaluate information about the introduced genetic construct as part of its evaluation of the biological product under the IND, and in most cases will also evaluate the genetic construct under an INAD, FDA will coordinate these submissions to avoid duplication. As stated above, the agency is considering developing guidance to clarify the circumstances in which it will expect a sponsor to submit information under an INAD and the circumstances in which it will expect a sponsor to submit information under an IND.

When a manufacturer wants to move past the investigational stage, it must get a BLA. As part of the BLA, the manufacturer must submit detailed information concerning manufacturing methods and processes. 21 CFR 601.2(a). These manufacturing methods would include development, use, maintenance, and eventual disposition of the biopharm animal. The Guidance for Industry for the Submission of Chemistry, Manufacturing, and Controls Information for a Therapeutic Recombinant DNA-Derived Product or a Monoclonal Antibody Product for In Vivo Use (1996, <http://www.fda.gov/cber/gdlns/cmcdna.pdf>) outlines the information that should be submitted in a BLA that includes manufacture using a transgenic animal. Applicants submit the specifics of development, care, maintenance and disposal of the animals in the BLA. This information is even more detailed than that provided in the IND.

FDA would also inspect the manufacturing facilities, including farms, laboratories, and storage areas used for the maintenance of the transgenic animals. The inspections also cover quality control and quality assurance records involving the husbandry of the animals. The standard operating procedures covering all aspects of the husbandry of the transgenic animals will be inspected, as well as those covering personnel training, access to the facility and incident reporting. Those SOPs that are considered to be particularly significant may also be required to be submitted as part of the license application. FDA considers all of this information in its final evaluation of the product.

Once the product is licensed, the applicant is required to report any significant changes to the information contained in the BLA. 21 CFR 601.12. This would include any changes to the construct or the biopharm animal itself, as well as changes to the final product. Depending upon the type of change, the applicant may have to obtain approval from FDA prior to implementing the change. As long as the license is in effect, there will also be routine inspections by FDA to ensure that current good manufacturing practices (GMPs) are being followed and that all required reports have been made appropriately.

FDA intends to coordinate requirements, and avoid duplications, in any situations where sponsors of biopharm animals need both an NADA and a BLA, and expects to address this issue in guidance. In broad strokes, the agency expects that the process would work as follows, recognizing that details would change with circumstances.

☐ In general, during the research stage of development of a transgenic biopharm animal producing a human biologic, a sponsor would have to file an INAD with CVM. In particular, INADs would be needed for non-laboratory feral animals that pose containment issues (such as fish in net pens (see Case Study No. I)), and for any animals that a sponsor would *propose* to dispose of through slaughter or rendering for human food or animal feed. CVM would inform FSIS of its decision regarding disposition.

☐ Once the sponsor was ready to conduct human clinical trials with the extracted purified biologic, sponsors would submit an IND to CBER. If the clinical studies and other information showed that the product was safe, pure, and potent CBER would issue a BLA for the human biologic under the PHS Act. If the license holder wanted the animal to be slaughtered or rendered for food or feed at the end of its productive life, he or she would need FDA approval, likely in the form of an NADA filed under the FFDCa. In such cases, to avoid unnecessary duplication, CVM and CBER would cooperate in the reviews of the animal drug (the inserted genetic construct) and the human biologic (the protein), and their possible effect on safety of the animal for food or feed. CVM would inform FSIS of its decision regarding disposition.

Because permitting an INAD or IND to go into effect and approving a new animal drug or BLA are federal actions under the National Environmental Policy Act (NEPA), the INAD, IND, BLA and NADA processes must comply with NEPA. These processes require preparation of an environmental assessment (EA), or the existence of a categorical exclusion from the requirement to submit an EA. 21 CFR 25.15, 21 CFR 511.1(b)(10), 21 CFR 601.2(c)(2).

In addition, as noted above, the FFDCa gives FDA authority to consider the environmental effects of a new animal drug on the health of humans and other animals, and the FFDCa and PHS Act give FDA authority to consider the environmental effects of a human biologic on human health. In both instances, FDA considers both direct and indirect effects.

FDA will examine the potential for environmental impacts in an EA and, if necessary, require mitigations for any potential impacts that would adversely affect human or animal health. Additionally, there may be applicable environmental requirements with respect to runoff from animal production facilities and land receiving animal waste under the Clean Water Act and other statutes. Waste generated from the processing of milk into biologics would also be regulated by the EPA in the same way that it regulates other pharmaceutical manufacturing facilities.

Farms housing biopharm animals are subject to all federal, state, local and Tribal laws pertaining to agricultural waste. These laws include rules defined by state environmental protection departments, Tribal governments, the USDA, and Natural Resources Conservation Service (NRCS). In addition, sponsors have internal Institutional Animal Care and Use Committees composed of professionals with varied backgrounds such as scientists, physicians, veterinarians, and ethicists, with some members from outside

institutions and the community. These committees oversee and approve research protocols, herd maintenance and herd health programs. This helps to ensure that the facilities operate in accordance with all environmental and animal welfare regulations and guidelines.

3. Hazard identification and risk assessment

General

Because transgenic animals are contained and carefully monitored, it is unlikely that animals would escape into the environment. In the event that animals escape, passage of the DNA in an inheritable form could only occur by breeding (e.g., goats with other goats). If such breeding occurred, the transgene could be passed to offspring and be expressed in the milk of lactating females.

Potential environmental effects of transgenic animals and their products

Potential adverse effects on the environment by domesticated biopharm animals such as goats generally would include those associated with non-transgenic varieties of such animals. Any additional potential adverse environmental effects would depend on the nature of the modification. There is little likelihood that the kinds of modifications discussed in this case study would cause domesticated biopharm animals to pose additional environmental risks beyond that of unintentionally passing the modification to conventional counterpart animals through mating. The transgene itself is an isolated segment of DNA. It would be no more likely to be taken up and incorporated into the genome of other organisms than any other piece of DNA of the animal, and so would have no different direct or indirect impact on the environment.

The human protein secreted into the milk by itself poses limited toxic risk to the environment. If the milk is accidentally spilled, the transgenic protein would be rapidly degraded along with other milk proteins. In general, transgenic proteins in these systems are expressed primarily in the milk of the animal and are not present in significant amounts in meat, stool, urine or other secretions. If sponsors were to intend to dispose of such animals through slaughter or rendering, then protein expression and potential biological effects would need to be evaluated in tissues to be used as food or feed.

FDA has used several resources to identify the hazards and environmental safety issues associated with biopharm animals. FDA staff includes scientists with expertise in animal husbandry, infectious disease, molecular biology, environmental science, food safety, and gene expression. Many FDA scientists continue to do laboratory research in these areas and to publish in scientific journals. FDA staff has training and expertise allowing identification and assessment of potential environmental hazards associated with the use of transgenic animal systems for production of therapeutic proteins. In addition, FDA scientists consult with outside experts, attend scientific conferences and public meetings, and stay apprised of recent developments in the scientific literature. FDA has published several guidances, such as the guidance mentioned above on the

manufacture and testing of therapeutic products in transgenic animals, that have been recently developed through expert working groups that provide information pertinent to identifying the hazards and environmental safety issues associated with transgenic animals.

FDA representatives have attended and given presentations at workshops and public meetings to obtain stakeholders concerns associated with critical issues, including the environmental impact of transgenic animal use. For example, FDA representatives consulted with Health Canada at the 1998 Consultation on Regulating Livestock Animals and Fish Derived from Biotechnology. This consultation involved intensive efforts to identify hazards and environmental safety issues associated with transgenic animals as well as test methods, risk characterization criteria and risk management recommendations. As needed, FDA also involves experts in other government agencies in its identification of hazards and safety issues on a national and local level. Advisory committees and ad hoc committees might also be used to address relevant questions in a public forum, as they have been in other instances

FDA staff consider a wide variety of issues in their scientific reviews, including: animal health, diseases susceptibility, zoonotic potential, animal welfare, animal husbandry, impact on domestic and wildlife populations, ability to survive in a farm environment, monitoring, and disease screening capabilities. Transgenic animals may have differing environmental effects depending on their fitness, interaction with other organisms, role in ecosystem or potential for persistence. In addition, FDA consults the Guideline for Ecological Risk Assessment (1998), that was developed by the Environmental Protection Agency, in order to assess environmental safety and risks associated with transgenic animals. In the process, FDA appraises the need for appropriate testing and information collection. Once the risks have been characterized, any necessary risk management is considered and included to determine whether risks can be minimized or eliminated.

4. Information and data

FSIS has published several policy documents regarding slaughter of transgenic research animals. FSIS explained its responsibility regarding safety, wholesomeness, and proper labeling of meat and poultry food products derived for animals subjected to the techniques of biotechnology in: Federal Register, Vol. 51, No. 123, Thursday, June 26, 1986 - "Final Policy Statement for Research and Regulation of Biotechnology Processes and Products." FSIS further elaborated its policies in two additional documents. Federal Register, Vol. 56, No. 249, Friday, December 27, 1991 - "Livestock and Poultry Connected with Biotechnology Research." and Federal Register, Vol. 59, No. 52, Thursday, March 17, 1994 - "Update on Livestock and Poultry Connected With Biotechnology Research."

FDA has published documents that describe the kinds of information and data generally needed to support applications. Guidance for manufacturing and testing is provided in Points to Consider in the Production and Testing of New Drugs and Biologics Produced by Recombinant DNA technology (1985), and in a guidance for the

Manufacture and Testing of Therapeutic Products for Human Use Derived from Transgenic Animals (1995) http://www.fda.gov/cber/ptc/ptc_tga.txt. Guidance for investigations under INADs are provided in Guidance for Industry Submitting a Notice of Claimed Investigational Exemption (1/99) <http://www.fda.gov/cvm/guidance/guidance.html>.

These guidance documents outline information to be collected, recorded and submitted by the sponsor in the IND and INAD applications. This includes characterization of the transgene construct and expression system, characterization and analysis of the transgenic founder animal and method of gene introduction. Other important information includes genetic stability and location of gene expression and information on the generation and selection of the production herd, including animal history, genealogy, and breeding techniques.

The guidance documents describe maintenance of animals, including monitoring the health of the animals, feeding, housing facilities, and disposal of animals. They also address information on product characterization, including methods of product recovery and definitions of product lots. Products are analyzed for adventitious and potentially infectious endogenous agents, which may arise from the host animal or tissue. Pathogen testing in the animals and milk products are described and protocols and data for elimination are presented. The product is analyzed for biochemical identity, purity, and potency. Lot release testing is described and data provided along with preclinical safety evaluation. All this information is submitted in the IND and is reviewed by product specialists, environmental scientists, veterinarians, biochemists, physicians trained in clinical trial design and other scientific and regulatory experts.

Data on different aspects of animal and product development are generated by the sponsor and then submitted in the IND or INAD, subsequent amendments, and BLA and NADA submissions. FDA staff review these data and if necessary consult with advisory committees when specific issues arise regarding the safety and efficacy of the product. Recommendations from internal review are transmitted back to the sponsor for clarification and response. The agency may inspect manufacturing facilities and take appropriate actions as necessary. The agency has the legal authority, technical capacity and resources to assess whether the sponsor is following specified regulations and procedures for manufacturing and using these products.

5. Mitigation and management considerations: approvals and conditions on research, development, production, distribution, marketing, use and disposal

Management practices designed to mitigate environmental risk include raising, identifying, and maintaining transgenic animals in specialized facilities that minimize contact of the transgenic herd with people, other animals, insects, and infectious agents. These facilities include physical and biocontainment capabilities.

In addition to FDA requirements pertaining to research and marketing of transgenic animals, sponsors are subject to requirements and oversight by Institutional Biosafety Committees and Animal Care and Use Committees (described above), and

generally are covered by the NIH Guidelines for Recombinant DNA Technology. These guidelines are mandatory for government funded research, and also are generally followed by industry.

The transition from research and development to production and distribution of a therapeutic product is covered by the IND, INAD, BLA and NADA. FDA has the legal authority under the FFDCAs and PHS Act to prevent studies from proceeding under an IND and to prevent further use of a product if it determines that appropriate conditions for product manufacture and clinical development are lacking. FDA maintains the appropriate legal, regulatory, and scientific expertise to identify and respond to environmental threats that affect health posed by transgenic animals by placing conditions on the development, production, distribution, marketing, use and disposal of transgenic animals. Under certain circumstances, EPA or FSIS may also have oversight authority of appropriate disposal of transgenic animals.

6. Monitoring and consideration of new information

FDA has the legal authority, technical capacity and resources to establish monitoring requirements for marketed drug or biologic products and such products under investigation. With input from local, state and federal environmental agencies, sponsors develop and implement individual programs to monitor for environmental effects during development of the product. The monitoring of the manufacturing facilities and farms is performed primarily by the sponsor and investigators, and they submit the data they collect to the agency for review. FDA staff performs inspections of the research and manufacturing facilities, the primary data, and the clinical sites. FDA can utilize outside experts within the federal government and non-government experts on advisory committees for input into these programs depending on the specific product.

7. Enforcement and compliance

Certain SOPs on various aspects of manufacturing are required to be in place before FDA will authorize the start of clinical trials. If FDA finds a critical SOP to be inadequate, FDA has authority to stop the clinical trial until the SOP is fixed. SOPs that are believed to be particularly critical to the purity, potency or safety of the product may be included in the BLA. If a license-holder violates such an SOP, FDA has the authority to suspend or revoke the license, and impose civil and criminal penalties. If a license-holder wishes to change one of these critical SOPs for a licensed product, he or she usually must first obtain FDA approval for the change. Such approval is not required if the SOP is not specifically included in the BLA or if FDA has determined that changes to that SOP have a minimal potential for adverse impact (21 CFR 601.12).

If a sponsor establishes, in an IND, SOPs for managing environmental risks to human health during the investigational phase of product development, or in a BLA for licensure of the product, the sponsor is required to follow those procedures for continued IND authorization or licensure. If the sponsor fails to follow its written SOPs for mitigation or monitoring of the environmental risk to health prior to or during

development of the product, the IND can be put on clinical hold. This means that no additional activity could occur under the IND until the FDA is satisfied that the safety issues have been addressed. If the agency were to discover that previously agreed-upon procedures were not being followed prior to licensure of the product, FDA has the authority to withhold approval of the license until the problems were resolved. This would mean that the sponsor could not market the biological product. If the sponsor were found to have failed to comply with environmental safety procedures after licensure, it would be subject to suspension or revocation of its license. 21 CFR 601.5, 601.6. FDA has authority to impose civil or criminal sanctions for this behavior.

A sponsor of a biological product under an IND is required to submit an annual report to FDA. 21 CFR 312.33. Such annual reports have to include information on steps the sponsor has taken to comply with any proposed mitigation or monitoring activities included in the IND. Inspections of the sponsor's facility may occur at any time during the development and marketing of products under an IND or BLA. Prior to BLA approval, an inspection of the manufacturing facility, which would include the animal area, would be performed to ensure that all procedures or facility features described in the BLA were in effect.

If the sponsor makes minor changes in its safety procedures (including environmental safety), it must report them in an annual report. 21 CFR 601.12(d). A sponsor may not make major changes (as described in 21 CFR 601.12(b)) in its safety procedures without receiving prior approval from FDA. Manufacturing plant inspections are scheduled every two years after licensure. However, FDA will inspect more frequently if there is cause to do so.

8. Public involvement and transparency

Public involvement in the development of a specific human biologic, whether through the use of transgenic animals or via more conventional manufacturing methods, is somewhat limited. Generally speaking, the agency has not disclosed information about specific licensure or approval applications, including the fact that a license or approval has been applied for, until after a decision has been made, and has not disclosed the existence of an IND or INAD unless the sponsor has publicly disclosed it, because FDA has considered this information to be confidential commercial information. In addition, SOPs generally constitute confidential commercial information. This limits the amount of public information and input possible for products prior to approval. The agency is considering whether there may be mechanisms by which it could make public its NEPA analyses, or components of its NEPA analyses, of products for which there is considerable public interest, and invite public comment prior to approval.

The agency does hold public workshops and advisory committee meetings to address scientific issues relevant to specific biological products. Notices of these events are published in the Federal Register and on the FDA web site. Public comment is encouraged at these on proposed regulations and guidances before enactment. In addition FDA informs the public using press releases on the approval of products and with letters

to industry on a variety of product safety issues. In addition, as mentioned previously, FDA and FSIS intend to encourage public discussion of public policy implications of disposal of biopharm animals through slaughter or rendering.

Currently, at the time of approval of a BLA and at the time of publication in the Federal Register of a notice of approval of an NADA, certain information in the application is available for public disclosure. This information can include safety and effectiveness data, study protocols, and environmental documents. In some cases, FDA makes such information available via its website. At this point, a member of the public could submit a Citizen Petition that requests withdrawal of approval of the application. At any time after the approval, new information that has a bearing on the approval of the NADA or BLA can be brought to the agency by anyone in the form of a Citizen Petition. FDA considers the information submitted, replies to the Petition, and takes appropriate action based on its reply that could include withdrawal of approval of the NADA or BLA, following applicable procedures.

SIDEBAR No. IV.A

FARM ANIMAL THAT PRODUCES ANIMAL BIOLOGICS

Overview

The Animal and Plant Health Inspection Service (APHIS) is involved in regulating health issues relating to transgenic animals in two situations. First, APHIS has authority to regulate "animal or veterinary biological products" that are produced in transgenic animals as biopharmaceuticals. APHIS anticipates that a small number of such biopharmaceutical animals will be developed in the near future.

Second, APHIS would regulate "biological products" that confer disease resistance, as when a "biological product" confers specific immunity when expressed in the blood the transgenic animal. Expression of immune proteins (antigens, antibodies, or other immune proteins) in nonbiopharm food animals are near physiological levels and otherwise are commonly present in animal blood and tissue. By contrast, expression levels of such proteins in the milk of biopharm animals would be considerably higher. Veterinary biological products confer immunity through a specific immune response. Certain cytokines are "veterinary biologics" when they are involved in the stimulation of a specific immune response.

There is currently considerable discussion within the agency as to the appropriateness of regulating under the Virus Serum Toxin Act (VSTA, 21 U.S.C 151-159, as amended by the Food Security Act of 1985) the transgenic "animal" itself as opposed to the "biological product" that is expressed in such animal. APHIS has current authority to regulate the purity, safety, potency, and efficacy of the "biological product" that confers specific immunity under the VSTA and regulations. These regulations, however, do not specify procedures for the field testing, licensure, or postlicense monitoring of the transgenic "animal" even though the animal may be the source of the "biological product" addressed under the regulations. APHIS believes that this regulatory gap should be addressed under new authorities that allow regulation of the "animal". APHIS is currently seeking new authorities under its Animal Health Protection Act that would largely help fill this gap in APHIS authorities. Reference to transgenic "animal" in the following discussion addresses the "animal" that expresses the "biological product" to confer specific immunity. The following discussion focusses on "biological products" expressed in transgenic food animals that confer specific immunity.

1. Description of the proposed organism/product and its use.

The proposed article would be a "biological product" that had been expressed in a farm animal to produce protection against a specific disease by means of an immune response. Transgenic animals bearing such "biological products" may be used in APHIS animal disease control programs, by farmers, veterinarians, or for export to foreign nations. Protection against specific disease would be expected to provide economic benefit and preclude the introduction or dissemination of animal disease. The use of such

animals would be expected to have trade benefits for the United States and other nations that utilized such animals.

Certain species of cattle may exhibit naturally occurring resistance to disease. Traditional selection for such resistance traits requires several generations of breeding and as many or more years of time. Transgenic animals exhibiting similar traits would be produced in shorter time periods for use on farms and in breeding operations.

No adverse effects on the environment are anticipated through the introduction of an animal expressing a "biological product" that confers immunity against specific disease. To the contrary, the "biological product" conferring immunity against specific disease would be expected to offer a positive benefit on the human environment through reduced economic loss, carcass disposal, and dissemination of disease.

The rationale for developing transgenic animals with a "biological product" conferring immunity against specific disease is to improve the health and well being of animals in addition to preventing economic loss due to animal disease. Transgenic animals may be developed, for example, with specific immunity against pathogenic strains of microorganisms that are not otherwise susceptible to known antibiotics. In addition, transgenic animals may provide specific immunity against disease, such as bovine spongiform encephalopathy (BSE), when no vaccine is available. A "biological product" such as an antibody that is targeted against specific prion proteins to prevent communicable disease would fall under the definition of a veterinary "biological product".

Constitutive expression of an immunoglobulin transgene in a farm animal species as a model to confer protection against specific disease was reported nearly 10 years ago (Lo, D. et al, Eur. J. Immunol. 21:1001-1006 (1991)).

2. Relevant Regulatory Agencies

A "biological product" that conferred protection against an animal disease based on a specific immune response and that had been expressed in a food animal would be licensed under the Virus-Serum-Toxin Act. APHIS would evaluate the product based on purity, safety, potency, and efficacy under the VSTA and regulations (9 CFR 101-118). Field testing of the experimental "biological product" that had been expressed in a food animal would be conducted under 9 CFR part 103. APHIS would review the genetic insert as part of the licensing process.

The Animal Quarantine Laws (AQL, 21 U.S.C. 101-135) and regulations under 9 CFR 122 ensure that farm animals and their progeny do not introduce or disseminate communicable disease. These statutes and regulations are administered by APHIS and would be applicable to transgenic farm animals. Because a "biological product" may be a component of an infectious agent, APHIS has to ensure that the animal bearing the "biological product" does not pose a risk of infectious disease.

As for any animal exposed to communicable disease, a transgenic animal infected with a live virus may be deemed a "vector" and may be issued a permit (hereinafter "permitted") for interstate movement. Alternatively, cells that are infected with genetic material derived from other organisms may be deemed "organisms" regulated under 9 CFR 122. Interstate movement would be prohibited under 9 CFR 122 for an organism or vector that had not been permitted or that contained a live "biological product", organism, or vector that posed a risk of introduction or dissemination of a contagious disease. In addition, the importation of animals would be permitted under 9 CFR 122 based on animal disease risk.

In the case of transgenic food animals, slaughter would be overseen by the Food Safety and Inspection Service (FSIS) under 21 U.S.C. 601 et seq. and regulations under 9 CFR 309.17 and 381.75. An MOU exists between APHIS and FSIS regarding the presence of a "biological product" in a food animal.

For a "biological product" that is expressed in a transgenic animal and that is not otherwise categorically excluded APHIS' regulations implementing the National Environmental Policy Act (7 CFR part 1b and 372), an environmental assessment would be prepared for field testing and licensure of the "biological product". Since transgenic farm animals other than fish or birds would normally be kept in the pasture or confined to the barnyard, no significant adverse impact on the human environment over their nontransgenic counterparts would be anticipated. For example, transgenic barnyard animals produced with a gene for growth hormone are not known to be significantly larger than their nontransgenic counterparts. Except for transgenic animals expressing animal biologics in their milk, most, if not all, of the transgenic farm animals expressing "biological products" licensed by APHIS would be for food production and therefore would be subject to slaughter approval by the Food Safety and Inspection Service.

Applications would be received by APHIS for the field testing, interstate movement, and licensure (for commercialization) of the "biological product" expressed in the transgenic farm animal. In addition, APHIS is currently implementing a national animal identification program under the AQL to facilitate APHIS's disease control and eradication programs. Such an animal identification program extended to transgenic animals would aid in the identification of genetically modified farm animals for such regulatory activities as interstate movement, import and export permits, animal health certification, disease control and surveillance, identification of biopharmaceutical animals, and slaughter approval.

Currently, the Virus-Serum-Toxin Act and regulations under 9 CFR 101-118 apply to recombinant and nonrecombinant animal biologics (vaccines, bacterins or bacterial antigens, allergens, antibodies, antitoxins, toxoids, antigenic components of live organisms, and diagnostic components for animal disease). The definition of a "veterinary biological product" would include a DNA-recombinant product that, when expressed in the transgenic farm animal, would render the animal resistant to disease.

The Animal Welfare Act (21 U.S.C. 2131-2159) and regulations (9 CFR 112) would also apply to transgenic food animals derived from experimental research. The care and housing of such animals would be considered, as would the affliction, if any, of pain and distress in the production of the transgenic animal.

3. Hazard Identification.

Under the Virus-Serum-Toxin Act and regulations, an applicant for a "biological product" license must demonstrate purity, safety, potency, and efficacy of the product prior to licensure. The applicant must demonstrate, based on appropriate tests, that the product is safe and efficacious for its intended use. The agency has extensive experience in the field testing and licensure of live recombinant animal vaccines, including live virus gene-deleted marker vaccines (Category II product under the 1986 Coordinated Framework for Biotechnology; see 51 Fed. Reg. 23339, 1986) and their companion diagnostic kits and live viral-vectored animal vaccines (Category III product under the 1986 Coordinated Framework).

Safety of "biological products" pertains to freedom from properties causing undue systemic reactions when used as recommended by the manufacturer (9 CFR 101.5(d)). The standard here is based on host animal response to administration of the "biological product".

In the case of live recombinant viral vectors, characteristics of safety and transmission must be examined before questions and concerns dealing with safety to humans, animals, and the environment can be answered and before such products can be considered for licensing (51 Fed. Reg. 23339, 1986). The licensing process would be intended to ensure that such live viral vector were no longer capable of transmissible disease.

Genomic DNA may also be transfected directly into a variety of mammalian cells. Alternatively, in such cases, the stable transfected cells could be considered as Master Seed (51 Fed. Reg. 23340, 1986). Tests to characterize the product may be required to demonstrate consistent gene expression (51 Fed. Reg. 23341, 1986).

Primary cells and cell lines used for production of Master Seed or vaccines must be tested in accordance with 9 CFR 113.51 and 113.52 for freedom from extraneous agents and characterized to establish genetic stability. Tumorigenicity and oncogenicity tests must also be conducted on cell lines if direct or indirect evidence indicates that the cell may induce malignancies in the species for which the product is intended (49 Fed Reg. 50899, 1984).

Efficacy of "biological products" pertains to the ability of the "biological product" to effect the result for which it is offered when used as recommended by the manufacturer (9 CFR 101.5(g)). The standard is based on comparable products prepared under a Standard Requirement for that class of product. It is anticipated that an

analogous Standard Requirement would be prepared for "biological products" that are expressed in the transgenic animal.

APHIS Animal Health Programs regulates the health of livestock animals. The National Center for Import and Export approves the international movement of animals and animal products based on disease risk. APHIS endorses the health certificates issued for such international movement and performs risk assessments in response to requests to regionalize areas of the world for freedom from animal disease.

APHIS National Animal Health programs is also involved in control of major diseases of farm animals including pseudorabies, brucellosis, bovine tuberculosis, and scrapie.

APHIS National Veterinary Services Laboratory prepares reagents and performs diagnostic testing related to animal disease. Plum Island Foreign Animal Disease Laboratory conducts tests and research for animal diseases exotic to the United States.

Consultations continue between APHIS, the FDA, and FSIS regarding issues of food safety.

The agency is represented on the Office Internationale des Epizooties (OIE, the principal international organization for world animal health) International Animal Health Code Standards Commission and Diagnostic Test and Vaccines Standards Committee. The agency is thus involved in international harmonization of standards for animal health and biologics.

APHIS experience would be directly applicable to the regulation of transgenic farm animals. This experience includes the licensure of recombinant live virus animal vaccines and vaccines for fish, environmental risk assessment and approval of recombinant vaccines for field testing and commercialization, control of diseases of farm animals and poultry, animal health certification and risk assessment for international movement of animals and animal products including fish based on disease risk.

4. Information and data.

The applicant for a "biological products" license would be required to submit data or relevant references from the scientific literature that the "biological product" is safe and efficacious for its intended use, e.g., to prevent specific disease.

Data obtained from host animal challenge studies would be required by APHIS to demonstrate that the "biological product" is efficacious for its intended use, i.e., that it protects against infection by a specific microorganism or protects against specific disease. Safety studies in the host animal would be required to demonstrate that the "biological product" poses no danger to the host animal or its progeny.

Prior to the issuance of a permit to field test a "biological product" derived from a live animal virus, APHIS would require an environmental assessment prepared under the National Environmental Policy Act (42 U.S.C. 4321-4335) and Council on Environmental Quality regulations (40 CFR 1500-1508) and guidelines (46 Fed. Reg. 18206, March 23, 1981).

5. Mitigation and management considerations

APHIS would require a permit under 9 CFR 122 for the interstate movement or importation of DNA-recombinant product expressed in a transgenic food animal based on disease risk. APHIS would issue a permit for the interstate movement or importation of such products expressed in animals.

If APHIS finds that such transgenic animal were affected with or had been exposed to an infectious disease, APHIS would prohibit the interstate movement or importation of such animal, as it would with a nontransgenic animal. APHIS may issue an order that such affected or exposed animal be moved directly to a slaughter facility or disposed of in a manner acceptable to APHIS. (9 CFR parts 50-99, and 122).

APHIS would issue a permit for the field testing of an experimental "biological product" that had been expressed in a transgenic animal (9 CFR 122) or licensure of a "biological product" expressed in such animal under 9 CFR 101-118.

A license may be revoked upon a finding that the "biological product" poses a danger to domestic animals (9 CFR 105).

6. Monitoring

APHIS veterinary biologics field operations would license production establishments and monitor postlicensing issues related to "biological products" expressed in transgenic animals. During the licensing process, APHIS Animal Health programs would be consulted regarding incorporation of transgenic animals into disease control programs. APHIS would ensure that transgenic animals bearing a licensed "biological product" did not pose a risk of disease transmission.

Veterinary Services would endorse animal health certificates for the export of transgenic animals expressing "biological products" licensed by APHIS. State Animal Health authorities may also be involved in monitoring the animal health status of transgenic animals.

7. Enforcement and compliance

APHIS Animal Health Statutes and regulations provide, among other enforcement authorities, for inspection of biologics facilities for compliance with APHIS regulations, detention and condemnation of worthless "biological products", civil and criminal

penalties, revocation of permits or licenses for violations of the VSTA and regulations, and disposal orders for contaminated animals and animal products under the AQL.

Public Involvement and Transparency

APHIS regulations pertaining to transgenic organisms are subject to Notice and Comment rulemaking including public notification and comment during the rulemaking process. APHIS has held public meetings related to biotechnology policy for recombinant vaccines prior to policy implementation or rulemaking. Draft environmental assessments are subject to public comment prior to preparation of a final environmental assessment under NEPA (7 CFR 1b and 372). Unless otherwise exempted, environmental assessments with opportunity for public comment are prepared prior to field testing or licensure of a recombinant veterinary "biological product".

APHIS intends to issue guidelines with opportunity for public comment regarding its policy related to transgenic farm animals.