Northwest Power and Conservation Council

January 27, 2011

To: Council Members

From: Steve Crow

Re: Presentation by the Food and Drug Administration on genetically engineered salmon

At Tom Karier's request, we invited a representative from the Food and Drug Administration to explain their review of genetically engineered salmon. Genetically engineered salmon are currently under review by the FDA and if approved, would be the first transgenic animal approved for human consumption. Alan Bennett, Public Affairs Specialist for the Seattle District of the FDA, will provide the Council with additional information about this issue. He is expected to discuss the decision being considered by the FDA, information on what the FDA decision will be based on, and the safeguards proposed to prevent any adverse effects on natural fish populations.

Enclosed is some background material on this presentation.

Enclosure

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The Legal Basics

1938 Food and Drug and Cosmetic Act

Definition of a drug

> (g)(1) The term "drug" means (A) articles recognized in the official United States Pharmacopoeia, official Homoeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them; and (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) **articles (other than food) intended to affect the structure or any function of the body of man or other animals**; and (D) articles intended for use as a component of any article specified in clause (A), (B), or (C). A food or dietary supplement for which a claim, subject to sections 403(r)(1)(B) and 403(r)(3) or sections 403(r)(1)(B) and 403(r)(5)(D), is made in accordance with the requirements of section 403(r) is not a drug solely because the label or the labeling contains such a claim. A food, dietary ingredient, or dietary supplement for which a truthful and not misleading statement is made in accordance with section 403(r)(6) is not a drug under clause (C) solely because the label or the labeling contains such a statement.

The Structure of FDA

Center for Food Safety and Applied Nutrition
Center for Drug Evaluation
Center for Biologics Evaluation
Center for Devices and Radiological health
Center for Veterinary Medicine
Office of Regulatory affairs

Why Center for Veterinary Medicine?

Issues from NAS Report Animal Biotechnology: Identifying Science-Based Concerns (2002)

- Food safety
  - New proteins – allergenicity
  - Bioactive molecules to enhance trait such as growth or disease resistance
  - lower concern – retain bioactivity after consumption?
  - Toxicty least concern because food safety assessment would identify
- Environmental Concerns
  - Transgenic animal becoming established
    - Ability to escape and disperse in diverse communities
      - Mobility, ease of feral
    - Fitness in environment
- Animal Health and Welfare

From our website

http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/VeterinaryMedicineAdvisoryCommittee/ucm222635.htm

How does FDA evaluate GE animals?

In the overall process described in GFI 187, FDA examines (1) safety of the rDNA construct to the animal; (2) safety of the food from the animal; (3) environmental impact; and (4) the extent to which the producers of GE animals (referred to as "sponsors") have met the claims made for those GE animals (effectiveness). All of these are based on a thorough analysis of the rDNA construct, its integration into the animal's DNA, and its stability in the animal over multiple generations. GFI 187 describes this in seven steps that we summarize in the following discussion. Each step is dependent on the results of the analysis performed in the preceding steps, so that the review in effect "rolls up" conclusions as it progresses through the entire process.

First, we review data and information on how the construct is made, and whether it contains any pieces of DNA from viruses or other organisms that could pose adverse health risks to the fish or people or other animals eating the fish. We evaluate the rDNA construct to determine whether pieces of DNA came from viruses that could intermix with similar viruses (in that species or other species with which it has close contact) and perhaps create a new virus that could pose health risks, similar to the way that avian flu arose. We also look to see if any pieces of the construct will make new proteins (except for the intended ones) that could possibly cause health concerns. GFI 187 refers to this analysis as the "Molecular Characterization of the Construct."

Second, FDA evaluates studies submitted by the producer to determine what happens when the rDNA construct is incorporated into the animal, and how it behaves over multiple generations in what GFI 187 refers to as the "Molecular Characterization of the GE Animal Lineage." This includes analyzing whether the construct remains in the same place over time, and whether animals continue to express the trait (characteristic) that the construct is supposed to introduce.

Third, FDA determines whether the rDNA construct is safe for the resulting line of GE animals by performing what GFI 187 refers to as the Phenotypic[2] Characterization. We do so by reviewing studies that characterize the actual GE animals over several generations. Questions that the agency asks include whether the resulting GE animals look like their "regular" counterparts by comparing them to both closely related animals and to animals of the species in general. The agency asks whether the GE animals are healthy, including disease resistance, and whether they reach the same developmental milestones that comparison animals do. Another safety question that is evaluated is whether there are any abnormalities that would not be found in other relatives of the Ge animal which might express similar traits, but via conventional breeding. For example, if an rDNA construct were introduced to make the animal grow faster, would close relatives that had been selected to grow faster via other assisted reproductive technologies or

natural breeding show any effects that could be due to fast growth? In addition, we are evaluating the results of necropsies (examinations of the bodies and tissues of animals that have been sacrificed for that purpose) to make sure that cells, tissues, and organs look normal. We also assess the results of the kinds of tests that doctors might perform on people when they get a physical, such as blood cells, blood chemistries, etc., to determine whether the animals not only look healthy, but also that their bodies are functioning appropriately. We evaluate the actual chemical composition of edible fish tissues to make sure that there are no substances in the tissues that could harm the GE animal or people who eat it, if it is intended for food use.

Fourth, we perform what GFI 187 calls a Durability Assessment. This reviews the plan that the sponsor will agree to in order to ensure that the GE animals produced in the future will be equivalent to the GE animals that we evaluate as part of the pre-approval review. This involves returning to some of the data presented in the characterization of the lineage of GE animals described in the second step, to ensure that the rDNA construct remains stable in multiple generations of the GE animal, and reviewing the plan that the sponsor is proposing in order to monitor subsequent generations of the GE animals.

Fifth, if the GE animal is intended to be used as a source of food, FDA assesses whether it is safe to eat the GE animal. This evaluation relies on information gathered in the parts of the application that look at the rDNA construct and the health of the animal. FDA experts in food safety look carefully at the composition of the edible tissues of the GE animal to determine whether its meat or milk or eggs differ in any way that affects safety or nutrition from the non-GE counterparts that we eat today. These experts evaluate whether the levels of key substances such as proteins, fats, minerals, and vitamins are in the same range as they are in the food we eat from conventional animals. If there are any differences, FDA must determine that there is a reasonable certainty of no harm from any of those differences.

In addition, FDA's food safety experts evaluate data to determine whether the GE animal poses any more allergenicity risks than its non-GE counterparts currently on the market. There are eight food groups that cause about 90% of all of the food allergies that people have. These include peanuts, tree nuts (such as almonds, filberts, and Brazil nuts), milk, eggs, wheat (not to be confused with gluten intolerance), soy, finfish, and shellfish. If the GE animal is one to which people already tend to be allergic, it is likely that they would avoid that species in order to avoid an allergic reaction. For example, if people are allergic to shrimp, they would not likely eat GE shrimp. Regardless, in this part of our evaluation, we will look to see whether the GE animals are more allergenic –that is, pose more of an allergic risk, than their non-GE counterparts.

Sixth, the agency evaluates the environmental assessment associated with the conditions proposed to raise the GE animal. As part of the approval process, the agency must meet the requirements of the National Environmental Policy Act (NEPA). NEPA requires that all federal agencies evaluate whether certain actions (in this case, the approval of a GE animal) will have an impact on the environment. Except in those circumstances where an environmental assessment (EA) is not required because the type of action does not have a

significant impact on the environment, we do this by evaluating the results of an environmental assessment (EA) for the specific conditions of use of a particular application. If we find, based on a review of the EA, that there is no significant impact on the environment under those conditions, we publish a Finding of No Significant Impact (FONSI). The EA is a public document. If we do find that there is an impact, a considerably more extensive assessment is required—the Environmental Impact Statement, in which the nature of the anticipated impact(s) are reviewed in detail.

There have been some concerns about the effects that intentionally released or escaped fast-growing fish would have on wild stocks of Atlantic salmon. When FDA approves a new animal drug application for a GE animal, it will generally be for a specific set of conditions of use. For GE animals, this includes the location and containment conditions. **Containment** is a term that encompasses any technique that keep animals from leaving a physical space, or that keeps them from interbreeding with other populations.

There have been some concerns about the effects that intentionally released or escaped fast-growing fish would have on wild stocks of Atlantic salmon. When FDA approves a new animal drug application for a GE animal, it will generally be for a specific set of conditions of use. For GE animals, this includes the location and containment conditions. Containment refers to keeping animals from leaving a physical space, or from establishing a population in an undesirable location.

There are a number of containment strategies. Containment systems that have multiple overlapping controls are more secure than those that have single controls. Three different types of containment strategies that are used in overlapping form for growing fish (including those that have not been genetically engineered) are:

1. **Physical containment.** Fish are kept in a different physical environment either in a different location or by using physical barriers. For example,
    a. Sea-dwelling fish raised in inland tanks far from the ocean
    b. Physical barriers (e.g. screening) placed at possible points of escape for small fish, such as water and waste pipes
    c. Netting placed over tanks to keep fish from jumping out or, if outdoors, to keep fish-eating birds from preying on them.
2. **Geographic/Geophysical containment.** Taking advantage of climate and other conditions, e.g., by siting an aquaculture facility in conditions unfavorable for fish to survive if they were to escape, such as still, silty, and warm water for a fish that needs high dissolved oxygen content and low temperatures.
3. **Biological containment**, which is generally thought of as a way to limit the spread of a population, and includes
    a. Inducing sterility. Pet owners exercise biological containment by neutering their cats and dogs. Many fin- and shell-fish are made sterile by inducing "**triploidy**" so that the cells that make eggs fail to develop properly (see Figure 4).
    b. Using only a single-sex population of the animal as the production animal.

Figure 4: What is Triploidy?

Triploidy is a form of "biological" containment. It is a way to make the population largely sterile. Most of the cells in the bodies of animals are diploid—they have two sets of chromosomes, one from their female parent and one from their male parent. Gametes, the male and female sex cells (eggs and sperm) are haploid—they have only one set of chromosomes. Triploid cells or organisms have three sets of chromosomes.

Triploid organisms can occur naturally, often in plants: bananas, apples, seedless watermelons, ginger, and some citrus are triploid, for example. Triploidy can occur naturally in some fish. Although it has not been successfully induced in birds or mammals, it can be induced in fish by treating fertilized eggs for a brief time with extreme physical means (higher than normal pressure or different temperatures, either warmer or colder than usual). Examples of fin- and shell-fish in which triploidy has been induced include oysters (food and pearl), mussels, scallops, clams, shrimp, trout, salmon, sea bream, tilapia, and catfish.

Triploidy is often employed in animals that are used for food for several reasons including wanting to have a sterile population. Most triploid animals are sterile because they don't reach sexual maturity and cannot produce sperm or eggs. Sexual maturation requires a great deal of energy, energy that can otherwise be used for growth. Finally, sterility is a way of keeping organisms from reproducing, thereby avoiding the possibility of their establishing a population in an ecosystem in the event of an unanticipated escape, or preserving intellectual property.

Fish scientists have looked carefully at the difference in texture, color, and composition in both diploid and triploid Atlantic salmon and have found that any difference that may be detected is due to variability between individual fish, and not because some fish are triploid and some are diploid (Bjornevik et al. 2004).

In the seventh and final step, that sponsors submit in support of their claims for the GE animal. (For conventional article regulated as drugs, this is referred to as "effectiveness.") For example, for the GTC goat, FDA determined that the goat did indeed produce human

antithrombin in its milk. For an animal that is intended to grow faster, the agency will need to evaluate data that shows that the GE animals do indeed reach some size or weight more rapidly than their conventional counterparts.

What information about this evaluation will be released to the public?

FDA will present the key information that the agency has evaluated, with any confidential information redacted, to the Veterinary Medicine Advisory Committee at a public meeting to be held on September 20, 2010. FDA anticipates making the meeting materials available approximately two weeks before this meeting, but in any event no later than 2 business days before the meeting.

Guidance for Industry 187

http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM113903.pdf

Environmental Issues

http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/VeterinaryMedicineAdvisoryCommittee/UCM224760.pdf

The likelihood of escape, establishment, and spread of *AquAdvantage* Salmon is extremely small due to redundant containment measures, including physical, physico-chemical, geographic/geophysical, and biological measures, that are being implemented at the sites of egg production, grow-out, and disposal. The combination of these various methods results in a very high degree of effective control. Physical measures include multiple mechanical means to prevent escape (e.g., screens, filters, etc.), while physico-chemical measures include the use of chlorine to kill any potential escapees. A strong management operations plan ensures that these containment measures are reliably implemented. Geographical and geophysical containment is provided by the location of the egg production and grow-out sites: the environment surrounding the egg-production site in Canada is inhospitable to early-life stages of Atlantic salmon due to high salinity; and, the environment downstream of the grow-out site in Panama is inhospitable to all life stages of Atlantic salmon due to high water temperatures, poor habitat, and physical barriers (e.g., several hydro-electric facilities). Biological containment is accomplished through the production of all-female triploid fish, which reduces the chance of breeding with native species, and significantly reduces the risk of transgene propagation in the environment.

Labeling Issues

Section 201(n) of the act provides additional guidance on how labeling may be misleading. It states that labeling is misleading if it fails to reveal facts that are material in light of representations made or suggested in the labeling, or material with respect to consequences that may result from the use of the food to which the labeling relates under the conditions of use prescribed in the labeling, or under such conditions of use as are customary or usual. While the legislative history of section 201(n) contains little discussion of the word "material," there is precedent to guide the agency in its decision regarding whether information on a food is in fact material. Historically, the agency has generally interpreted the scope of the materiality concept to mean information about the attributes of the food itself.

Under current law, FDA does not have the authority to require labeling based on consumer interest alone. For example, in *Stauber v. Shalala*, the court explained that, absent evidence of a material difference between milk from rBST-treated cows and non-rBST-treated cows, the use of consumer demand as a rationale for mandatory additional labeling would violate the law.[

In *Alliance for Bio-Integrity v. Shalala*, a coalition of groups and individuals challenged FDA's decision not to require additional labeling of foods from GE organisms. The plaintiffs alleged, among other things, that FDA's failure to require additional labeling for foods from the GE plants was arbitrary and capricious. Further, the plaintiffs claimed that the process of genetic modification was a material fact, and FDA should have considered the widespread consumer interest in having foods made from GE organisms labeled.

The court denied the plaintiffs' claims, deferring to FDA's determination that, in general, genetic engineering does not materially alter foods. Further, the court held that consumer demand alone was not sufficient to require additional labeling of foods made from GE organisms. The court explained that only when "materiality has been established may the FDA consider consumer opinion to determine whether a label is required to disclose a material fact." The court held that "[g]iven these facts, the FDA lacks a basis upon which it can legally mandate labeling, regardless of the level of consumer demand."

Genetically Engineered Animals

FDA

New traits can be introduced into animals. Here's how it works for animals engineered to produce a human pharmaceutical.

1

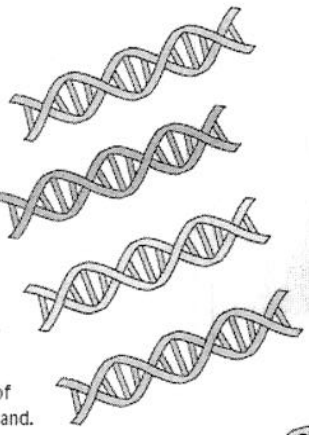
Generation of the DNA Construct

A. Milk Protein Promoter DNA: Allows for expression only in goat mammary glands.

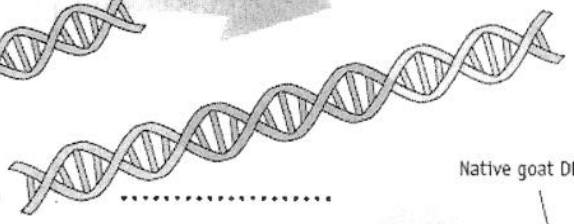
B. Therapeutic Protein Gene: Encodes a protein known to treat disease in people.

C. Terminator Sequence: Assures that only the gene of interest is controlled by A.

D. Other DNA Sequences: Helps with the introduction of the new combination DNA strand.

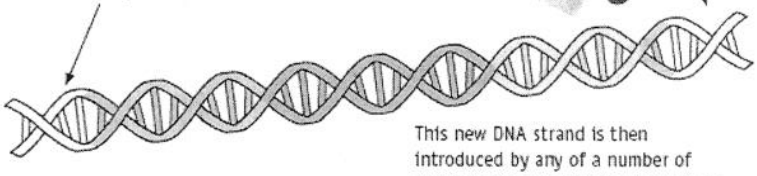


2 The DNA construct is created by combining A, B, C and D.



Native goat DNA

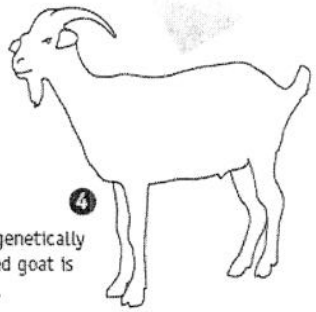
3



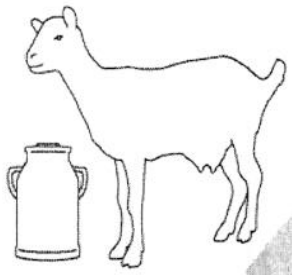
Native goat DNA

This new DNA strand is then introduced by any of a number of methods into an animal cell, such as an egg, that is then used to produce a genetically engineered animal.

4 The first genetically engineered goat is produced.



5 The offspring of the first genetically engineered goats, referred to as production animals, are milked. The milk is transferred to a purification facility.



6 The drug to be used to treat human disease is purified from the goat's milk.