FDA on transgenic animals—a dog's breakfast?

To the editor:

On January 15, the US Food and Drug Administration (FDA) finally published its risk assessment regarding the safety of milk and meat products from cloned animals and their offspring (http://www.fda.gov/cvm/cloning.htm). The situation is not as rosy, however, when it comes to transgenic animals. After 20 years of dithering, the agency has not yet managed to publish a policy statement concerning animals containing a gene from another organism introduced by recombinant DNA techniques. But Larisa Rudenko, a senior official in the FDA's Center for Veterinary Medicine (CVM), has given a strong hint of the agency's preferred approach.

It is not good news. Rudenko said at Bio 2007 in Boston, MA, that every new genetic construction in an animal that employs gene-splicing technology would require approval for use in the food supply, and that the applicable procedures and regulations would be the same as for drugs used to treat animal diseases.

But the introduction of a gene is not the same as the administration of a drug. Not for the first time, FDA is trying to force a square peg into a round hole. Moreover, the CVM's approach represents a major shift in FDA's regulation of biotech that will be hugely expensive to animal breeders and detrimental to consumers. When I discussed this in Washington, DC, with John J. Cohrssen, who worked on FDA reform during the 1990s as majority counsel of the US House Commerce Committee, he characterized FDA's new approach as "complex, arbitrary and dilatory." Until now, FDA has not regulated farm animals or even animals used for what might be termed 'medical purposes'. For example, if German shepherds or golden retrievers were bred to enhance traits that made them better seeing-eye or companion dogs, the FDA would not regulate them under its medical device regulations. Nor would a leaner line of pigs be regulated differently from others under the FDA's food regulations, unless some safety issue were raised. Likewise, for transgenic animals used in medical research, the FDA has not asserted jurisdiction over the hundreds of transgenic rodent lines that are available.

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Despite protests from activists, such as these on their way to demonstrate against the FDA's Draft Risk Assessment on Clones at Washington, DC's Capitol building last February, the FDA decided in January that such foods may be sold and consumed. FDA should now rethink its approach, stop its foot-dragging and promulgate a definitive, science-based policy on transgenic animals.

The most apposite models for gene-spliced, or transgenic, animals are the agency's oversight of traditional foods and food additives; and the production of livestock clones, or identical twins, which FDA confirmed in January were safe to eat.

The only transgenic animal currently marketed to the public at large is the 'Glofish', a small, tropical, ornamental (aquarium) zebrafish that glows because of the insertion and expression of a gene (from another marine organism, the sea anemone) that synthesizes a beautifully colored fluorescent protein (http://www.glofish.com/)[1]. The FDA opted not to regulate this organism according to the following rationale: "Because tropical aquarium fish are not used for food purposes, they pose no threat to the food supply. There is no evidence that these genetically engineered zebra danio fish pose any more threat to the environment than their unmodified counterparts, which have long been widely sold in the United States. In the absence of a clear risk to the public health, the FDA finds no reason to regulate these particular fish." (It is noteworthy that in spite of the fact that Glofish are not eaten and would not survive outside an aquarium, they have been effectively banned by state regulators in California; http://www.fda.gov/bbs/topics/NEWS/2003/NEW00994.html.)

Especially if the standard for becoming subject to regulation is "a clear risk to the public health," that statement from the FDA would seem to weaken the argument for treating all transgenic animals used for food as though they were being treated with a new drug.

A company called Aqua Bounty Technologies (Waltham, MA, USA) has been trying for more than a decade to get FDA approval to market an Atlantic salmon that contains a newly introduced Chinook salmon growth hormone gene engineered to keep it turned on all year round (instead of during only the warmer months, as in nature). This cuts the time to marketable adult weight from 30 to 18 months. The extra gene confers no detectable differences in the salmon's appearance, taste or nutritional value; it just grows faster. In spite of sufficient evidence that the fish is safe to eat and does not differ nutritionally from other Atlantic salmon, the FDA has kept the company treading water for years, effectively condemning the commercial program to extinction.

There are numerous other applications in various stages of R&D, including transgenic livestock with leaner muscle mass, enhanced resistance to disease and improved use of dietary phosphorous to lessen the environmental impacts of animal manure. (The fluorescent zebrafish was first developed as a means of detecting environmental pollution; it was engineered to fluoresce in the presence of certain

toxins.) But if regulators don't soon begin to let sound science and common sense dictate their regulatory decisions, the entire animal biotech sector could virtually disappear.

Several kinds of problems plague the CVM. Perhaps because it has a lower profile than other FDA centers, it has difficulty attracting and recruiting personnel familiar with the nuances of modern molecular biology. Another problem is that the 'new drug' paradigm doesn't fit well for transgenic animals. A better model is the way that another FDA center, the Center for Food Safety and Nutrition, regulates other foods. The law places the burden of ensuring the safety of foods and food ingredients on those who produce them. It prohibits the adulteration (contamination) or misbranding (mislabeling) of food, but does not inspect or evaluate all food before its sale in shops, supermarkets or restaurants. Rather, FDA's oversight (which encompasses all food except meat, poultry and egg products, which are regulated by the Department of Agriculture) relies on market surveillance or postmarketing regulation, and the FDA takes action only if there is an apparent problem. Although not perfect, this approach has worked quite well over many years.

The law does require a premarketing review for certain food-related products. These include most food additives—a class of ingredients that includes preservatives, emulsifiers, spices and sweeteners, and natural and synthetic flavors or colors, among others. In general, a food additive must be approved if it becomes a component of or otherwise affects the characteristics of a food and it is "not generally recognized as safe (GRAS) by qualified experts for its intended use."

GRAS is an important concept: before a new food additive is marketed, it is the responsibility of the producer to determine whether or not the substance is GRAS. The agency routinely reviews food additive applications for safety only when the substance in question has been determined not to be GRAS by the producer. If the producer determines that a substance is GRAS, only a notification of that decision to the FDA is necessary (which is then subject to agency review).

Contrary to the statements of CVM official Rudenko, the FDA's existing approach to biotech and to foods in general could be adapted easily to transgenic animals. After all, in traditional applications, two GRAS substances that have been combined are still considered GRAS. Similarly, because adding a GRAS gene to a GRAS organism is likely to yield a GRAS outcome, an FDA premarketing review should not be necessary for genetic constructions like the fast-growing salmon. But instead the FDA intends to treat every new animal as though it contains a 'new drug', the evaluation of which can take many years (and delay the benefit to consumers), even if there is negligible likelihood of harm.

The GRAS/food additive concept is relevant to transgenic animals because of the nature of the techniques. Transgenic animals usually are created by injecting the desired gene—which may be intended to confer an advantage in husbandry or nutrition, for example—into a single-cell embryo or by inserting the gene into a skin cell and creating an embryo by a process called cloning. In either case, the embryo that now contains the foreign gene is then implanted into the uterus of a surrogate mother. If the foreign gene is incorporated into the DNA of the offspring, then like other genes it is passed on to succeeding generations, and the product of the gene (usually a protein) can be considered either GRAS or a food additive, depending on its function and other factors. These transgenic animals subsequently are propagated in conventional breeding programs.

The FDA's approach to 'novel' foods, published in 1992 (ref. 2), is compatible with the GRAS/food additive paradigm. It emphasizes that the Center for Food Safety and Nutrition does not impose discriminatory regulation based on the use of one technique or another, but that greater scrutiny is applied only when certain safety issues are raised. These include the presence of a completely new substance in the food supply, changes in a macronutrient, increase in a natural toxicant or the presence of an allergen where a consumer would not expect it. The application of similar criteria to the oversight of transgenic animals would go a long way toward the creation of a scientifically defensible, risk-based policy.

Officials at the FDA's CVM would likely counter that a newly introduced gene expressed in an animal is similar to the injection of a new drug, that the genetic modification mediates the introduction of the substance synthesized under the direction of the new gene—a hormone or enzyme, for example. Yet this theory ignores that neither the FDA nor any other government agency routinely conducts premarket review of new genetic constructions that occur 'naturally' (we call these 'mutants'). An example is the Zucker rat, a naturally occurring mutant that is more than four times the size of its normal siblings, and which is available from commercial breeders for the study of obesity, insulin resistance and a condition called 'metabolic syndrome'. Another more familiar example is the mule, a horse-donkey genetic hybrid, which, by any reasonable definition, is certainly transgenic, although it doesn't involve the use of newfangled genetic techniques. (The FDA has not asserted its regulatory authority over these or similar genetic constructions.)

Why would CVM adopt such a dubious and internally inconsistent policy? I would put forward three reasons. First, when they can, bureaucrats exhibit a tendency to arrogate new responsibilities and create new regulatory empires. "Dogs bark, cows moo and regulators regulate," FDA commissioner Frank E. Young once quipped. Second, the 'new drug' paradigm is the only vehicle available to CVM. (Recall the old adage, "When the only tool you have is a hammer, more and more problems begin to look like nails.") And third, the FDA is currently in the throes of a crisis in leadership. Senior officials have been indecisive and largely ineffective—and far more concerned about human drugs than other categories of products.

If animal biotech companies are to bring home the bacon, the FDA will need to provide a more thoughtful and science-based approach to their products. The statements coming out of CVM regarding the regulation of transgenic animals reflect a presumptive policy that is illogical and torturous. It would be better for the agency to delay a policy statement until it can offer a proposal that makes scientific, regulatory and common sense.

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