Genetically Engineered (GE) Animals: Background, Regulations, and Implications

Alison Van Eenennaam, Ph.D.

Cooperative Extension Specialist

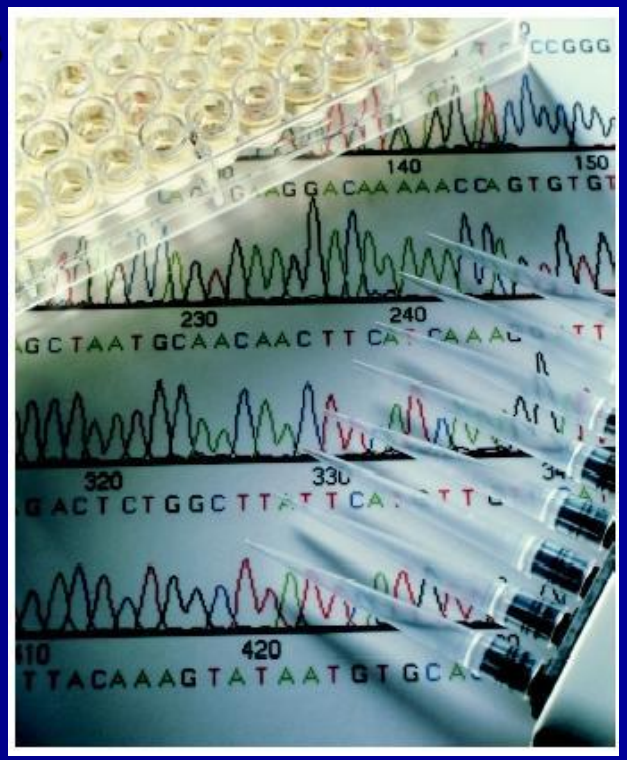
Animal Biotechnology and Genomics

Department of Animal Science

University of California, Davis

alvaneenennaam@ucdavis.edu

"The mission of the animal genomics and biotechnology extension program is to provide broad, science-based extension programming on the uses of animal biotechnologies in livestock production systems."



http://animalscience.ucdavis.edu/animalbiotech

Overview

- Timeline of genetically-engineered animals
- How are GE animals being regulated?
- What are GE animals being used for?
- The AquAdvantage GE salmon story
- Effect of regulatory gridlock on investment, US competiveness, geographical location of research and application of GE technology for animal agricultural applications

Timeline of genetically engineered (GE) animals in US

Year	Event
1980	• Genetically engineered (GE) mice
1985	• GE livestock and fish first created
1997	• Hello Dolly – Adult somatic cell nuclear (SCNT) cloning
2008	• FDA issues risk assessment on clones in the food supply
2009	• FDA guidance on how GE animals will be regulated using new animal drug approach • FDA approval of first GE animal pharmaceutical

rDNA
gene construct

embryo

transgenic animal

Research
- disease models

Biomedical
- pharmaceuticals
- xenotransplantation

Industrial

Agriculture
- none on market to date

Pharma and industrial applications of GE (or a combination of cloning & GE)

The first product from a transgenic farm animal to become a registered drug was Antithrombin III from GTC-Biotherapeutics, USA, produced in the mammary gland of transgenic goats for heparin resist-ant patients to prevent blood clots

Bio membership
Join, renew, or learn about BIO member benefits

Home
About BIO
Conferences & Events
Past BIO Events
Industry Calendar
State/Int'l Calendar
Members.BIO.org
BIOtech NOW
BIO Bulletins
Suggestion Box
Membership Directory
BIO Videos
News, Media, Speeches, & Publications
BIO Blogs & Podcasts
National Issues

News & Media > Press Releases >

FDA Grants First-Ever U.S. Approval of GE Animal Product Printer Friendly

For Immediate Release
2/6/2009

Contact:
Contact Karen Batra
202-449-6382

WASHINGTON, D.C. (Friday, February 06, 2009) - Advances in human health care from the genetic engineering of animals are now being realized in the United States. The U.S. Food and Drug Administration (FDA) announced today the first approval of a product derived from a genetically engineered (GE) animal.

ATryn®, a recombinant form of human antithrombin developed by GTC Biotherapeutics, was approved by the FDA for the prevention of peri-operative and peri-partum thromboembolic events in hereditary antithrombin deficient patients. It is not indicated for treatment of thromboembolic events in hereditary antithrombin deficient patients. ATryn® is the first ever transgenically produced therapeutic protein and the first recombinant antithrombin approved in the United States.

Along with the approval of ATryn®, the FDA's Center for Veterinary Medicine also approved GTC's New Animal Drug Application, the first of its kind to regulate GE animals. This is now required for a recombinant technology used to develop transgenic animals, such as the goats that produce recombinant antithrombin. GTC has granted OVATION the right to market ATryn® in the United States and pursue further clinical development.

February 2009, First GE Animal Product

www.gtc-bio.com

Cloned transchromosomic calves producing human immunoglobulin

Yoshimi Kuroiwa[1], Poothappillai Kasinathan[2], Yoon J. Choi[3], Rizwan Naeem[4], Kazuma Tomizuka[1], Eddie J. Sullivan[2], Jason G. Knott[2], Anae Duteau[3], Richard A. Goldsby[3], Barbara A. Osborne[5], Isao Ishida[1*], and James M. Robl[2*]

Published online: 12 August 2002, doi:10.1038/nbt727

Human polyclonal antibodies (hPABs) are useful therapeutics, but because they are available only from human donors, their supply and application is limited. To address this need, we prepared a human artificial chromosome (HAC) vector containing the entire unrearranged sequences of the human immunoglobulin (h*Ig*) heavy-chain (*H*) and lambda (*λ*) light-chain loci. The HAC vector was introduced into bovine primary fetal fibroblasts using a microcell-mediated chromosome transfer (MMCT) approach. Primary selection was carried out, and the cells were used to produce cloned bovine fetuses. Secondary selection was done on the regenerated fetal cell lines, which were then used to produce four healthy transchromosomic (Tc) calves. The HAC was retained at a high rate (78–100% of cells) in calves and the h*Ig* loci underwent rearrangement and expressed diversified transcripts. Human immunoglobulin proteins were detected in the blood of newborn calves. The production of Tc calves is an important step in the development of a system for producing therapeutic hPABs.

http://www.nature.com/naturebiotechnology

Transchromosomal cattle carry a human artificial chromosome harboring the entire sequence of the human major histocompatability complex . These animals were cloned from bovine fibroblasts after transfection with the additional chromosome.

www.hematech.com

Xenotransplantation 2010: 17: 48–60
Printed in Singapore. All rights reserved
doi: 10.1111/j.1399-3089.2009.00564.x

XENOTRANSPLANTATION

Pigs as organ donors

Structural characterization of α1,3-galactosyltransferase knockout pig heart and kidney glycolipids and their reactivity with human and baboon antibodies

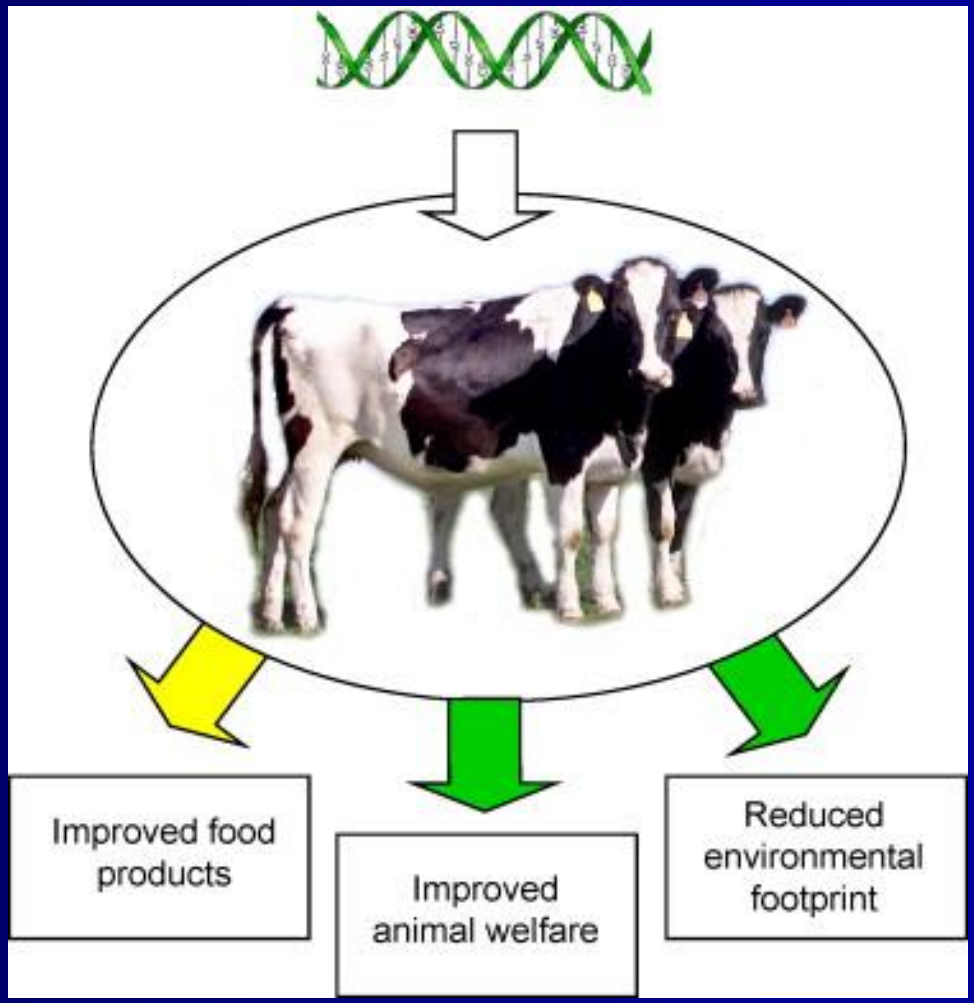
Diswall M, Ångström J, Karlsson H, Phelps CJ, Ayares D, Teneberg S, Breimer ME. Structural characterization of α1,3-galactosyltransferase knockout pig heart and kidney glycolipids and their reactivity with human and baboon antibodies.
Xenotransplantation 2010; 17: 48–60. © 2010 John Wiley & Sons A/S.

Mette Diswall,[1] Jonas Ångström,[1] Hasse Karlsson,[2] Carol J. Phelps,[3] David Ayares,[3] Susann Teneberg,[2] and Michael E. Breimer,[1]

[1]Department of Surgery, Institute of Clinical

www.revivicor.com

Genetically engineered animals for agricultural applications



Mastitis-resistant cows
(inflammation of mammary gland)

nature biotechnology

ARTICLES

Nature Biotechnology 23:445-451. 2005

Genetically enhanced cows resist intramammary *Staphylococcus aureus* infection

Robert J Wall[1], Anne M Powell[1], Max J Paape[2], David E Kerr[3], Douglas D Bannerman[2], Vernon G Pursel[1], Kevin D Wells[4], Neil Talbot[1] & Harold W Hawk[1]

Mastitis, the most consequential disease in dairy cattle, costs the US dairy industry billions of dollars annually. To test the feasibility of protecting animals through genetic engineering, transgenic cows secreting lysostaphin at concentrations ranging from 0.9 to 14 mg/ml in their milk were produced. *In vitro* assays demonstrated the milk's ability to kill *Staphylococcus aureus*. Intramammary infusions of *S. aureus* were administered to three transgenic and ten nontransgenic cows. Increases in milk somatic cells, elevated body temperatures and induced acute phase proteins, each indicative of infection, were observed in all of the nontransgenic cows but in none of the transgenic animals. Protection against *S. aureus* mastitis appears to be achievable with as little as 3 mg/ml of lysostaphin in milk. Our results indicate that genetic engineering can provide a viable tool for enhancing resistance to disease and improve the well-being of livestock.

http://www.nature.com/naturebiotechnology

www.ars.usda.gov

Omega-3 Pigs
(Pigs cloned after genetically engineering cell)

BRIEF COMMUNICATIONS

nature biotechnology

Nature Biotechnology 24:435-436. 2006

Generation of cloned transgenic pigs rich in omega-3 fatty acids

Liangxue Lai[1,2,8], Jing X Kang[5,8], Rongfeng Li[1], Jingdong Wang[5], William T Witt[6], Hwan Yul Yong[1], Yanhong Hao[1], David M Wax[1], Clifton N Murphy[1], August Rieke[1], Melissa Samuel[1], Michael L Linville[3], Scott W Korte[4], Rhobert W Evans[7], Thomas E Starzl[6], Randall S Prather[1,2] & Yifan Dai[6]

Meat products are generally low in omega-3 (*n*-3) fatty acids, which are beneficial to human health. We describe the generation of cloned pigs that express a humanized *Caenorhabditis elegans* gene, fat-1, encoding an *n*-3 fatty acid desaturase. The hfat-1 transgenic pigs produce high levels of *n*-3 fatty acids from *n*-6 analogs, and their tissues have a significantly reduced ratio of *n*-6/*n*-3 fatty acids ($P < 0.001$).

The health benefits of long chain *n*-3 fatty acids, found mainly in fish oils, are well recognized. Meat products normally contain small amounts of *n*-3 fatty acids and large amounts of *n*-6 fatty acids[1]

University of Missouri/Massachusetts General Hospital and Harvard Medical School

GE Chickens That Don't Transmit Bird Flu

Breakthrough could prevent future bird flu epidemics

Suppression of Avian Influenza Transmission in Genetically Modified Chickens

Jon Lyall,[1] Richard M. Irvine,[2] Adrian Sherman,[3] Trevelyan J. McKinley,[1] Alejandro Núñez,[2] Auriol Purdie,[3]* Linzy Outtrim,[2] Ian H. Brown,[2] Genevieve Rolleston-Smith,[3] Helen Sang,[3]† Laurence Tiley[1]†‡

Infection of chickens with avian influenza virus poses a global threat to both poultry production and human health that is not adequately controlled by vaccination or by biosecurity measures. A novel alternative strategy is to develop chickens that are genetically resistant to infection. We generated transgenic chickens expressing a short-hairpin RNA designed to function as a decoy that inhibits and blocks influenza virus polymerase and hence interferes with virus propagation. Susceptibility to primary challenge with highly pathogenic avian influenza virus and onward transmission dynamics were determined. Although the transgenic birds succumbed to the initial experimental challenge, onward transmission to both transgenic and nontransgenic birds was prevented.

The diversity of avian influenza viruses (AIVs) and their propensity for interspecies transmission make them a global threat to animal and public health communities. Cross-species transmission of influenza viruses mediate host species that amplify and diversify virus populations, notably domestic chickens, ducks, and pigs (*1*). Although control of AIV infection in its wild aquatic bird reservoir is impractical, control of AIV in domesticated hosts is

The diversity of viral antigenic sub-

Science 331:223-226. 2011 SCIENCE VOL 331 14 JANUARY 2011 223

www.roslin.ed.ac.uk/public-interest/gm-chickens

Fast growing salmon

The founder female was generated in 1989 – 24 years ago

Nature Biotechnology 10:176 – 181. 1992

GROWTH ENHANCEMENT IN TRANSGENIC ATLANTIC SALMON BY THE USE OF AN "ALL FISH" CHIMERIC GROWTH HORMONE GENE CONSTRUCT

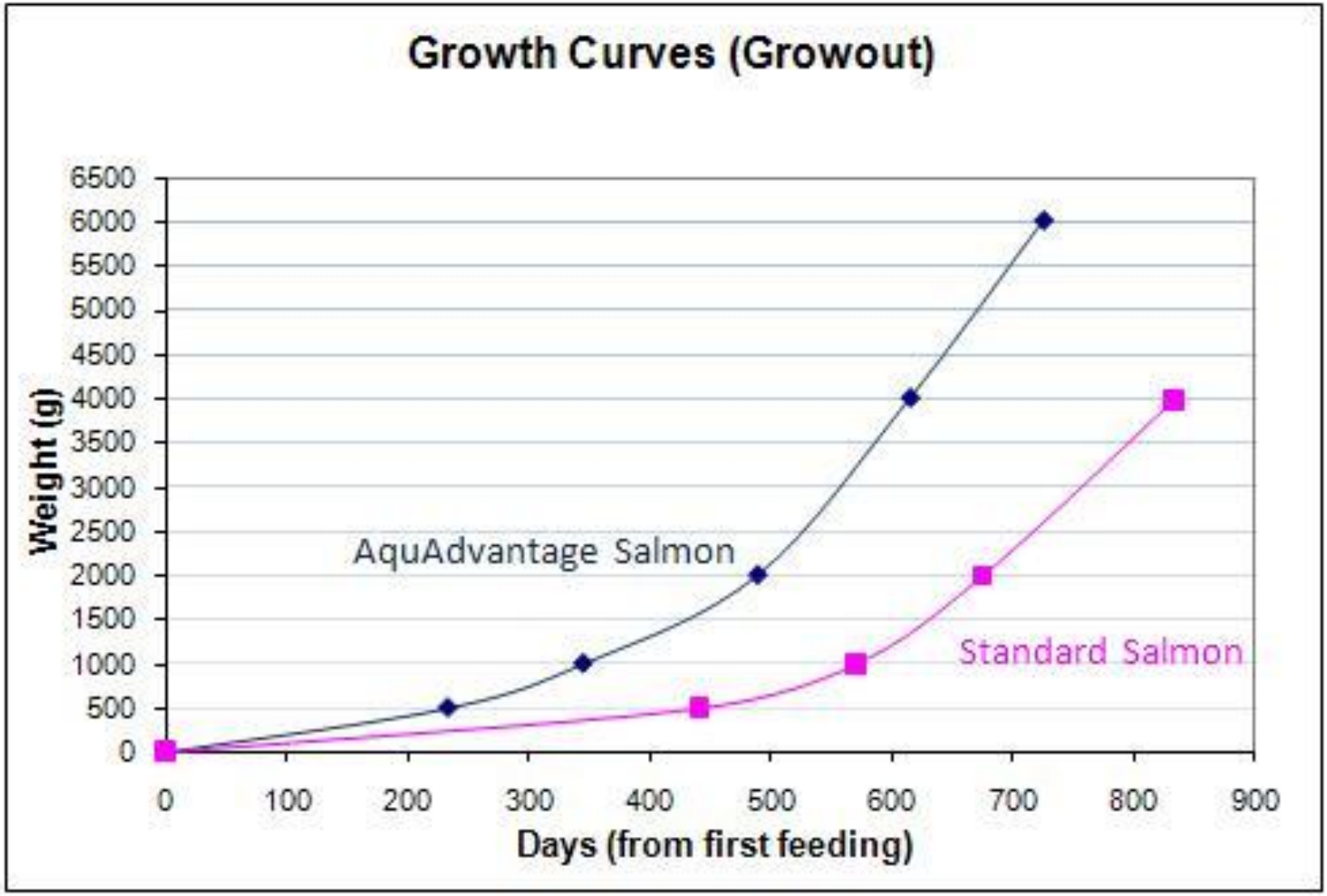
Shao Jun Du, Zhiyuan Gong, Garth L. Fletcher[1], Margaret A. Shears[1], Madonna J. King[1], David R. Idler[1] and Choy L. Hew*

Research Institute, The Hospital for Sick Children and Departments of Clinical Biochemistry and Biochemistry, University of Toronto, Toronto, Canada M5G 1L5. [1]Ocean Sciences Centre, Memorial University of Newfoundland, St. John's, Newfoundland, Canada A1C 5S7. *Corresponding author.

We have developed an "all fish" growth hormone (GH) chimeric gene construct by using an antifreeze protein gene (AFP) promoter from ocean pout linked to a chinook salmon GH cDNA clone. After microinjection into fertilized, nonactivated Atlantic salmon eggs via the micropyle, transgenic Atlantic salmon were generated. The presence of the transgene was

University of Toronto/Memorial University of Newfoundland, Canada

Fish reach adult size in 16 to 18 months instead of 30 months



In a letter to the FDA dated April 26, **1993**, AquaBounty Technologies (then A/F Protein) initiated discussions with the FDA seeking regulatory guidance for development and approval of a GE Atlantic salmon intended to grow faster than conventionally bred Atlantic salmon.

- In January 2009, the Food and Drug Administration issued a final guidance for industry on the regulation of genetically engineered (GE) animals (had 28,000 comments on draft!!)
- FDA plans to regulate GE animals under the new animal drug provisions of the Federal Food, Drug, and Cosmetic Act (FFDCA), and the National Environmental Policy Act (NEPA).

187

Guidance for Industry

Regulation of Genetically Engineered Animals

Containing Heritable Recombinant DNA Constructs

Final Guidance

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

“New Animal Drug” approach

- “Drugs are …articles…intended to affect the structure or function of the body of man or other animals”
- The expression product of the new construct (e.g. growth hormone) is also considered to be the new animal drug
- Application process requires that the developer demonstrate that no harm comes to individuals who use the drug under prescribed conditions

PEW 2003. Future Fish: Issues in Science and Regulation of Transgenic Fish

Date	Event
September 1995	AquaBounty submits Investigational New Animal Drug (INAD) application with FDA for fast-growing salmon with intent to commercialize
September 2010	Public Veterinary Medicine Advisory Committee (VMAC) meeting to consider data on safety and efficacy of AquAdvantage salmon Held in Washington DC

Product Definition for the AquAdvantage Salmon

Product Identity

Triploid hemizygous, all-female Atlantic salmon (*Salmo salar*) bearing a single copy of the transgene.

Claim

Significantly more of these Atlantic salmon grow to at least 100 g within 2700 deg C days than their comparators.

Limitations for Use

These Atlantic salmon are produced as eyed-eggs for grow-out only in the FDA-approved physically-contained fresh water culture facility.

FDA NEWS RELEASE

FOR IMMEDIATE RELEASE
January 15, 2009

Media Inquiries:
Michael Herndon, (301) 796-4673
Consumer Inquiries:
888-INFO-FDA

FDA Issues Final Guidance on Regulating Genetically Engineered Animals

En Español

The U.S. Food and Drug Administration today issued a final guidance for industry on the regulation of genetically engineered (GE) animals under the new animal drug provisions of the Federal Food, Drug and Cosmetic Act (FFDCA). The guidance, titled "The Regulation of Genetically Engineered Animals Containing Heritable rDNA Constructs," clarifies the FDA's statutory and regulatory authority, and provides recommendations to producers of GE animals to help them meet their obligations and responsibilities under the law.

Genetic engineering generally refers to the use of recombinant DNA (rDNA) techniques to introduce new characteristics or traits into an organism. When scientists splice together pieces of DNA and introduce a spliced DNA segment into an organism to give the organism new properties, it is called rDNA technology. The spliced piece of DNA is called the rDNA construct. A GE animal is one that contains an rDNA construct intended to give the animal new characteristics or traits.

"Genetic engineering is a cutting edge technology that holds substantial promise for improving the health and well being of people as well as animals. In this document, the agency has articulated a scientifically robust interpretation of statutory requirements," said Randall Lutter, Ph.D., deputy commissioner for policy. "This guidance will help the FDA efficiently review applications for products from GE animals to ensure their safety and efficacy."

The FDA released the draft guidance in September 2008 with a 60-day public comment period, and received about 28,000 comments. The agency has summarized and responded to these comments on the Web site listed below.

The FDA's Center for Veterinary Medicine (CVM) has been working with developers of GE animals on both early stage and more mature applications.

"At this time, it is our intent to hold public scientific advisory committee meetings prior to making decisions on GE animal-related applications" said Bernadette Dunham, D.V.M., Ph.D., director of CVM.

The FFDCA defines "articles (other than food) intended to affect the structure or any function of the body of man or other animals" as drugs. An rDNA construct that is in a GE animal and is intended to affect the animal's structure or function meets the definition of an animal drug, whether the animal is intended for food, or used to produce another substance. Developers of these animals must demonstrate that the construct and any new products expressed from the inserted construct are safe for the health of the GE animal and, if they are food animals, for food consumption.

The guidance also describes the manufacturer's responsibility in meeting the requirements for environmental review under the National Environmental Policy Act.

For more information:

- Genetically Engineered Animals

The public VMAC meeting held in Washington DC was intended to increase transparency, clarity, and public confidence in the GE animal regulatory process

Less than 2 weeks after the VMAC meeting, more than 40 members of Congress signed letters requesting FDA halt the approval of the Aqua Bounty transgenic salmon.

"The FDA's hastily completed approval process puts American consumers and the environment at risk. GE salmon could be devastating to fishing and coastal communities, our food source, and already depleted wild salmon populations. The FDA should put the interests and safety of American families and our ocean resources above special interests"

http://ge-fish.org/2010/09/29/thirty-eight-representatives-and-senators-call-on-fda-to-halt-ge-salmon-approval

Paradoxically it often seems that the arguments for and against GE animals for food purposes overlap

- Groups opposed to the technology argue that the risks GE animals pose to food safety, animal health, and the environment are too great to allow the technology to move forward.

- Proponents of the technology see the potential benefits for GE animals to produce safer food, improve animal health, and reduced environmental impact as too great to forgo the use of this technology in animal agriculture production systems.

Dr. Calestous Juma, Harvard's Kennedy School of Government, at a 6/23/11 hearing to examine the benefits of agricultural biotechnology held by the House Agriculture Committee's Subcommittee on Rural Development, Research, Biotechnology, and Foreign Agriculture

". . It is not this particular fish that is at stake. It is the principle behind the amendment (to prohibit use of FDA funds to evaluate any application for approval of genetically engineered salmon) and its wider ramifications. It sends the message to the rest of the world that the science-based regulatory oversight as embodied in the FDA review process is subject to political intervention.

Furthermore, it signals to the world that the United States may cede its leadership position in the agricultural use of biotechnology. . . I believe it is imperative that the United States stay the course it has set in not letting politics interfere with its science-based regulatory system that is truly the envy of the world."

Current Situation of AquAdvantage Application – 2 years after VMAC

- During 2011, an Environmental Assessment for the AquAdvantage salmon was reviewed by U.S. Fish and Wildlife , NMFS, and the USDA, all of whom found it to be acceptable
- Procedurally, the next step is for the FDA to release an Environmental Assessment (EA) given the proposed conditions of use which will either be associated with a “finding of no significant impact” (FONSI), or a finding of significant environmental impact.
- This would trigger a 60 day comment period following the release of the FDA’s Environmental Assessment (EA)
- There has been no formal comment or response from FDA or any other government body on the status of the application, or why it has not been acted upon in the 2 years following September 2010 VMAC meeting and VMAC report

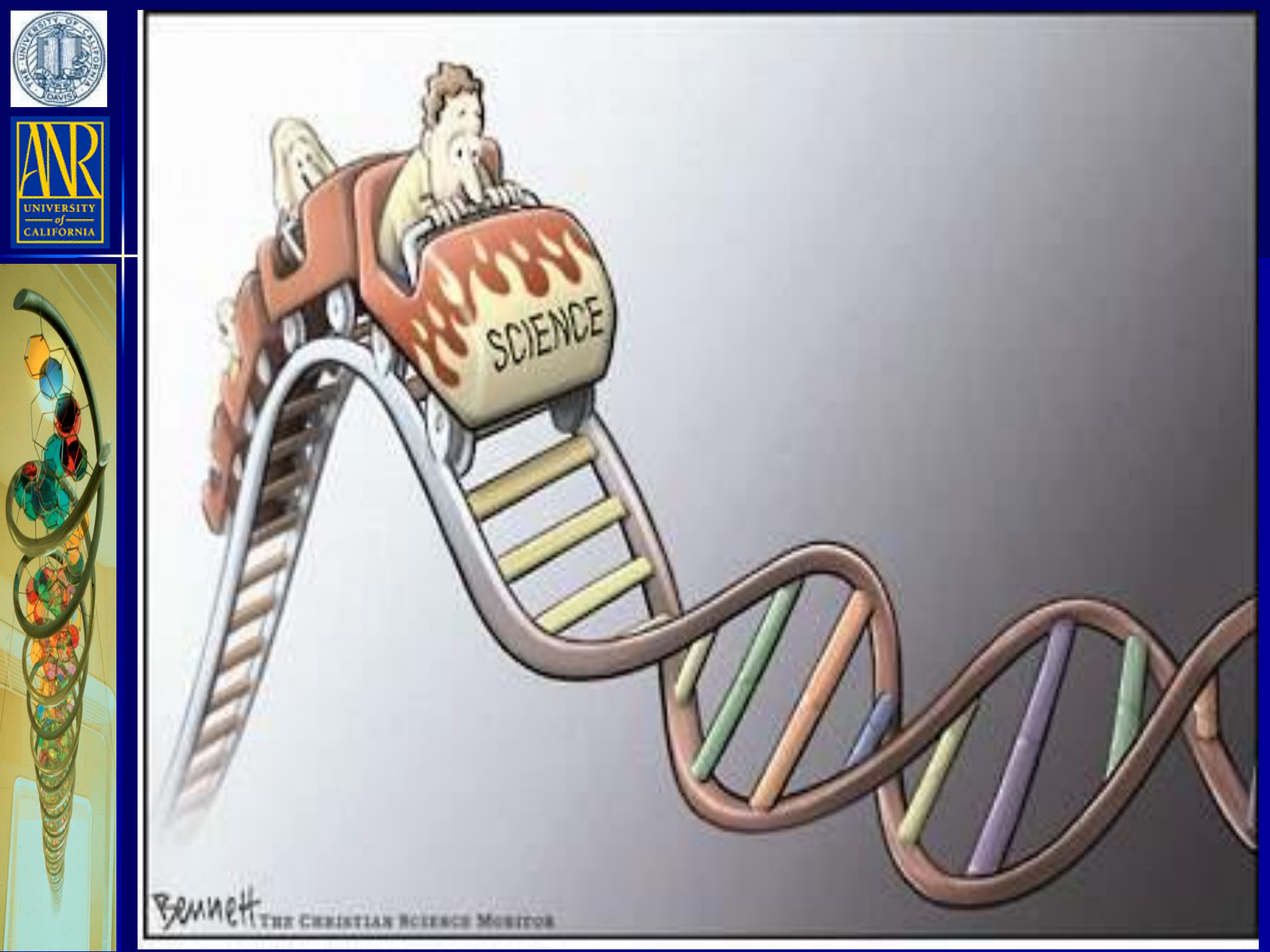
Timeline of GE animals for agricultural applications in US

Year	Event
1985	• GE livestock and fish first created
1995	• FDA review of AquAdvantage salmon begins
2001	• First regulatory study submitted by Aqua Bounty Technologies to U.S. FDA for a New Animal Drug Applications
2008	• FDA issues risk assessment on clones in the food supply
2009	• FDA guidance on how GE animals will be regulated • FDA approval of first GE animal pharmaceutical • Final AquAdvantage regulatory study submitted to FDA
2010	• FDA VMAC meeting on AquAdvantage salmon (9/20/10)
2011	• Political efforts to prevent FDA from regulating GE salmon
2012	• GE animals for non-food purposes growing industry and jobs • Still waiting for regulatory decision on AquAdvantage salmon • Delayed approvals decreasing investment in ag applications • Use of GE animals for food actively pursued in other countries

25+... years from discovery to application

Sites working on GE livestock for food – 1985
North America, Europe and Australasia

Sites working on GE livestock for food - 2012 Asia and South America are moving forward with this technology in their animal agriculture


SCIENCE
Bennett
The Christian Science Monitor