Veterinary Medicine Advisory Committee Meeting

AquAdvantage Salmon

September 19 - 20, 2010

Sunday, September 19, 2010

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U.S. Food and Drug Administration
Veterinary Medicine Advisory Committee Meeting
AquAdvantage Salmon
September 19, 2010

VMAC members present:

David F. Senior, ACVIMN-SA, ECVIM, VMAC Chair (Acting)
Craig Altier, D.V.M., Ph.D.
Michael D. Apley, D.V.M., Ph.D.
Dicky D. Griffin, D.V.M., M.S.
John B. Kaneene, D.V.M., Ph.D.
Jodi Ann Lapidus, PhD.
Alan G. Matthew, Ph.D.
James D. McKean, D.V.M., J.D.
Robert H. Poppenga, D.V.M., Ph.D.
Paul C. Stromberg, D.V.M., Ph.D.

Temporary Voting Members present:

Gregory Jaffe
Gary Thorgaard, Ph.D.
Alison Van Eenennaam, Ph.D.
Kevin D. Wells, Ph.D.

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I N D E X

I N D E X (cont.)

Keynote: "---" indicates inaudible in the transcript.
"*" indicates phonetically spelled in the transcript.

A F T E R N O O N S E S S I O N

(1:09 p.m.)

Welcome

by Bernadette Dunham, D.V.M., Ph.D., CVM Director

DR. DUNHAM: Well, good afternoon, everybody, and thank you very much for your patience. We really do appreciate you all coming over to participate in a very exciting two days of discussion as we welcome our Veterinary Medicine Advisory Committee meeting to a discussion on AquAdvantage Salmon. It is a beautiful day outside -- I wish we could be outside -- but thank you again for coming today.

This is really an exciting time for us. I think this technology is holding incredibly great promise specifically for the world's food supply. But we recognize that it is the first of its kind, and we truly are sailing on some uncharted waters. However, it will be the science that leads us forward as we chart these new waters.

We have an amazing group of scientists at CVM. As the Director for the Center for Veterinary Medicine, I am very proud to be able to work with such terrific colleagues, and you are going to have a chance to meet a few of them today and tomorrow. They have absolutely applied their vast expertise and careful, thorough review to the review of the data that will be presented.

We have had our most senior and experienced

reviewers analyze the data and the information that will be presented, and they have reached their conclusions unanimously at all risk-base stages of reviews. And I really want to personally thank each and every one of them for an outstanding job.

Now, this afternoon is going to be education. Tomorrow will be the VMAC Committee meeting that will listen and discuss and advise us, but today it is an opportunity to reach out and talk about this particular technology. And there is a full agenda this afternoon, as you can see. We are going to step you through this. You will have a chance to hear from each one of our key reviewers.

But right now, what I want to do is take advantage of introducing the fabulous folks that make up our Veterinary Medical Advisory Committee, and we are so pleased to have them here this afternoon.

Let me start with our Chair, which is Dr. David Senior, and David, if you wouldn’t mind, I would like you to stand because not everybody can see your nameplate. Dr. Senior is the Associate Dean, the Advancement and Strategic Initiatives, at the School of Veterinary Medicine at Louisiana State University.

I may be out of sync here, but we are going to follow all the way along, if I can do this correctly.

Dr. Craig Altier is Associate Professor, Department

of Population Medicine and Diagnostic Sciences, College of Veterinary Medicine, at Cornell University.

Dr. Mike Apley is Associate Professor, Department of Clinical Sciences, College of Veterinary Medicine, Kansas State University.

Our consumer representative -- is that him? -- is Dr. -- sorry, Mr. Greg Jaffe, Director of the Biotechnology Project, Center for Science in the Public Interest, here in Washington, DC.

Then we have Dr. -- hang on one second -- John Kaneene, who is University Distinguished Professor of Epidemiology, Center for Comparative Epidemiology, at Michigan State University.

We have Dr. Jodi Ann Lapidus, Assistant Professor, Division of Biostatistics, Department of Public Health and Preventative Medicine, Oregon Health and Science University.

Then we have Dr. Alan Mathew, who is Professor and head of the Department of Animal Science at the University of Tennessee.

We have Dr. Jim McKean, University Professor and Extension Swine Veterinarian, Department of Veterinary Diagnostic and Production Animal Medicine at Iowa State University.

We have Dr. Robert Poppenga, Professor of Clinical Toxicology, California Animal Health and Food Safety Lab,

School of Veterinary Medicine at the University of California at Davis.

We have Dr. Paul Stromberg, Professor of Veterinary Pathology, Department of Veterinary Biosciences, Ohio State University.

And we have Dr. Kevin Wells as our subject matter expert, Assistant Professor, University of Missouri, Animal Science Research Center.

We have Dr. Alison Van Eenennaam, Cooperative Extension Specialist, Animal Genomics and Biotechnology, Department of Animal Science, University of California at Davis.

And Dr. Gary Thorgaard, School of Biological Sciences and Center for Reproductive Biology at Washington State University.

So I am very, very pleased and I want to thank all of you for taking time out of your very busy schedules to participate and be able to advise us on this very important topic. I really do sincerely thank you for your time.

And so with no further ado, let me move forward now and I am going to have Dr. -- she is going to be our honorary doctor today -- Aleta is going to -- Sindelar -- is going to step us through most of the presentation this afternoon.

And while she is coming up, I have three quick announcements. Please turn off all cell phones while in the

Committee. Parking in the hotel is free today and tomorrow, and all tickets should be validated at the front desk. And finally, the session is being recorded, so I would ask that each one of you please announce your name for the public record. And on that note, Aleta, thank you so much.

The Role of the VMAC Committee Member

by Aleta Sindelar

MS. SINDELAR: Good afternoon, everyone. It is a pleasure to see all of our Committee members and subject matter experts here to support this very important Advisory Committee meeting. In addition, it is a new opportunity to welcome the public.

Our VMAC meeting members typically receive a general orientation to the logistics relevant to their membership as a special government employee to the Center for Veterinary Medicine. Also, their meeting management, travel and reimbursements, as well as particular regulatory provisions that may affect the Agency’s oversight of the general class of products under discussion.

The orientation does not discuss the particular matter at hand. Today’s orientation to the members is different. We will not focus on the logistics of our members’ participation but rather underscore the general roles and responsibilities of each member as an FDA/CVM special government employee participating in the CVM Advisory

Committee meeting.

I am beginning with the Agency we all know is the Food and Drug Administration, to talk about our mission, our vision, our leaders, our reviewers, our teams and your critical service to the Center in anticipation of this VMAC meeting.

To assist the FDA in its mission to protect and promote the public health, the FDA uses 49 committees and panels to obtain independent, expert advice on scientific, technical and policy matters. Members of the committees are screened for conflicts of interest. The following is the Conflict of Interest Statement for the Veterinary Medicine Advisory Committee meeting today and tomorrow:

"The following announcement addresses the issue of interest with regard to this meeting and is made part of the public record to preclude even the appearance of a conflict of interest at this meeting on September 19th and 20th, 2010.

"Federal conflict of interest laws preclude the participation of committee members and consultants in advisory committee meetings if they have a conflict of interest, unless a 'Waiver of Exclusion' is granted by the Agency.

"The Associate Commissioner for Special Medical Programs, FDA, has appointed Mr. Gregory Jaffe and Drs. Gary Thorgaard, Alison Van Eenennaam and Kevin Wells as Temporary Voting Members for this meeting.

"Based on the submitted agenda for this meeting and a review of all the financial interests reported by the Committee participants, it has been determined that all interests in the firms regulated by the Center for Veterinary Medicine, which have been reported by the participants, pose no potential for conflict of interest at this meeting.

"In the event that the discussions involve specific products or firms not on the agenda for which FDA's participants have a financial interest, the participants are aware of the need to exclude themselves from such involvement and their exclusions will be noted for the public record.

"With respect to all other meeting participants, we ask in the interest of fairness that that they address any current or previous financial involvement with any firm whose products they wish to comment upon." Excuse me.

(Slide)

The mission of FDA is to protect the public health by ensuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, the nation's food supply, cosmetics, and products that emit radiation.

(Slide)

Most Americans recognize FDA. The products we oversee account for nearly 20 cents of every dollar of consumer spending in this country. This amount is over

$1,000,000,000,000 worth of products.

FDA is in the news daily -- the recall of shell eggs due to Salmonella Enteritidis, seafood safety in the Gulf, FDA's ban on cigarettes containing certain characterizing flavors, and FDA's guidance on Federal menu labeling requirements. And with respect to CVM, you are all aware of the issues relating to antimicrobial resistance, H1N1, pet food recalls, totals in Salmonella, and more. Sorry -- I am not staying up with my slides! (Comments on managing slides) Okay, thank you.

(Slide)

We have strong leadership to pave the way to improving and approving new products and technologies. Dr. Margaret Hamburg is our Commissioner. Dr. Joshua Sharfstein is our Principal Deputy Commissioner. Mike Taylor is our Deputy Commissioner for Foods. And Dr. Bernadette Dunham is our Director for the Center. Each is a strong advocate for a rigorous scientific review and discussion of the issues subject to the purview of FDA's regulatory oversight.

(Slide)

On April 21st of this year, Dr. Hamburg spoke at the Food and Drug Law Institute. Her remarks contained three basic questions we must ask ourselves here at the FDA:

First, when confronted with a novel challenge in food and drug regulation, FDA must start with the science.

The first question we must ask is: What is going on? What does the science, the data, tell us?

But as the science evolved, the answers are relatively simple. New technologies and new products in both food and in health offer the potential for tremendous public health benefits.

Yet there are many -- there may be new or unique tasks that can affect certain populations and there are unanswered questions that must be considered and pursued. FDA needs to draw on the very best science as possible within the Agency and beyond to assess new challenges.

Dr. Hamburg pointed out as one of her priorities as Commissioner is to both increase FDA's science capacity and strengthen the broader field of regulatory science inside and outside of the Agency. This includes the utilization of FDA advisory committees in this process.

(Slide)

The second question we must ask is: What is the right policy approach to address the new challenge?

On the one hand, if there is a real risk to the American people and the risks clearly outweigh the benefits, the answer is easy -- the public needs to be protected. On the other hand, if we are dealing with a new product where the benefits far outweigh the risks, we should have the processes in place that facilitate a speedy approval.

But most often, the answer is somewhere in the middle, and based on the specific circumstance, we may need to perform additional assessments, provide advice to clinicians, or seek additional post-market studies to fashion the best ongoing approach.

(Slide)

The third, and final, question. Once we have our best possible grasp of the science and have identified the appropriate policy options, we must ask: How can the law help the Agency get as close as possible to the best solution?

No matter what the topic, there is a spectrum of legal options available to the Agency. On one extreme, the Agency can warn the public and attempt to remove products from the market. On the other, the FDA can explain its support for a product's safety and effectiveness even against erroneous attacks.

But there is also a great deal that falls between these two extremes, situations that are not easy to resolve and which require judgment to figure out the right path forward.

That is where the Agency's wide range of legal tools come into play. In this case and others, FDA should not be shy in pointing out where different legal approaches may provide the Agency with the authority to do its job well and credibly.

Recognizing the complexity of the challenges facing FDA and facing public health law is another way of recognizing the immense responsibility that this Agency has. We rise to that challenge by searching out the best possible science, identifying the right policy options, and then finding a legal path to move forward.

Here at CVM we rely on our scientists as well as our counsel. Laura Epstein, legal counsel to the Agency, is here today and tomorrow to provide important information on a regulatory framework. She is keenly aware of the options of the Agency with respect to its legal oversight of genetically engineered products.

(Slide)

CVM echoes the mission and vision of FDA. Our mission is to protect human and animal health. Our vision is excellence, innovation, and leadership.

(Slide)

When does FDA convene an Advisory Committee meeting?

The Agency has guidance describing when FDA convenes a meeting. In general, most meetings are convened to discuss products approvals, safety issues, labeling issues and other scientific issues such as FDA’s approach for assessing the human food safety risk of antimicrobials used in food animals.

(Slide)

What is the value of VMAC?

FDA obtains advice from scientific experts on product approvals, complex and unique issues, and post-market safety issues.

Very importantly, the VMAC is a process of transparency. This transparency shows the Agency's decision making process and the VMAC fulfills FDA's commitment to hold VMAC meetings for genetically engineered animal approvals as stated in CVM's Guidance 187 for genetically engineered animals.

(Slide)

The VMAC members' expertise is diverse, covering a wide range of specialties.

(Slide)

FDA supplements advisory committees with temporary voting members when specific expertise is required that is not available among current voting members. Particular expertise in genetic engineering has been added to our Committee as well as an individual who is highly recognized as a consumer advocate and serves as the consumer representative on our Committee.

(Slide)

I want to underscore that all members and temporary voting members have been fully reviewed for any conflicts of interest, all our participating and voting members for this meeting.

In general, what I would like to remind the members, for purposes of discussion tomorrow, are the responsibilities we see applicable.

(Slide)

We expect that you have read and are familiar with the Agency's briefing package and environmental assessment, that you are familiar with comments submitted to the Agency regarding the topic of the meeting, and to be familiar with the charge to the Committee and the questions that the Agency is seeking VMAC comments on.

We expect that you will participate actively, be prepared to ask questions from speakers and OPH -- Open Public Hearing -- participants after presentations, and to be prepared to make comments during the Committee deliberations.

(Slide)

I would also like to point out that this is a Particular Matters Meeting. This means we are intending to discuss a particular product made by a particular sponsor. This also means there is no discussion permitted outside of the VMAC meeting regarding this particular matter and this particular topic.

There are no press interviews until the meeting adjourns. And for the assistance of VMAC members and others who may be here, we have press officers from FDA. When I call your name, could you please stand, so they can recognize you?

Siobhan Delancey, FDA Press Officer. Pat El-Hinnawy, FDA Press Officer. Laura Bradbard -- she is here -- CVM Press. And Shannon Cameron, CVM Press Officer. She may be outside.

(Slide)

Today, we have a full agenda. You will hear from our Animal Biotechnology Interdisciplinary Group, referred as the ABIG, on genetic engineering for animals; our review process for genetic animals; the National Environmental Act; our Chief Counsel's Office about regulatory framework, and more from me regarding the deliberative process.

At the end of the day, there will be time for questions from the VMAC to the presenters. With time remaining, the public may be also able to ask clarifying questions to the speakers.

At this time, I would also like to publicly recognize the Animal Biotechnology Interdisciplinary Group and the AquAdvantage team who were responsible for the review of this application. Would everyone please stand to be recognized? Thank you very much.

(Slide)

From all of us here at CVM, we thank you for your interest in attending this meeting and supporting the Veterinary Medicine Advisory Committee in their efforts to provide scientific and expert comments to the Agency on this very important matter. Thank you.

DR. DUNHAM: Thank you very much, Aleta. You are going to see a lot of Aleta. She is absolutely fabulous and most of our VMAC members have interacted with her. She is definitely a star and we want to thank you so much.

It is my honor and privilege right now to move into the educational portion of this afternoon. And for that, we will have Dr. Larisa Rudenko. She is our senior advisor for biotechnology to the Center and she directs the Animal Biotechnology Interdisciplinary Group. Her training is in molecular biology and risk assessment and she has worked in developing methods for the assessment of safety of products of biotechnology for over 20 years. She is also a Diplomat of the American Board of Toxicology. Dr. Rudenko?

Genetic Engineering: An Overview

by Larisa Rudenko, Ph.D., DABT

DR. RUDENKO: Welcome, everybody. We are working off this, not a lavalier? Okay, all right.

Thank you for coming out on a beautiful Sunday afternoon. I know it is gorgeous outside and everybody would really rather be sitting in the park having a nice sandwich or something and a glass of wine, but you are here and we really appreciate it.

(Slide)

So what I am going to do today is give you the bird’s eye overview of genetic engineering just on the off

chance that someone here has not yet heard of genetic engineering and to let you know a little bit about how the genetic engineering of animals came about.

For those of you who are experts in the area, my apologies, and for those of you who may have forgotten a fact or two, perhaps this will be helpful. I would like to also thank Dr. Eric Schulze for helping me prepare the slides.

(Slide)

Okay, so what are we going to talk about today? Animals and humans, how animals and humans first started to get together and interact with each other.

I would like to give you some examples of developing technologies, give you a very brief overview of genetic engineering in modern biotechnology, how one produces a genetically engineered animal, and then finally leave you with a couple of conclusions that you can go away from the day with.

(Slide)

So, genetically engineered animals, some people call them transgenic animals. In Europe, they are referred to as genetically modified animals. Here in the United States, the FDA believes that genetically modified organisms can be modified by other techniques besides recombinant DNA and so we reserve the term “genetically engineered” for those organisms that have been modified by recombinant DNA technology. Codex

refers to these organisms as rDNA organisms, but here they are GE, not GM/GE, okay?

(Slide)

Genetically engineered animals are a reality; we have already approved one. For those of you who missed it, it was on February 6th, 2009, and it was a goat that produced a human therapeutic drug in its blood, and so we approved the goat, the FDA -- CVM approved the goat and CVR approved the human therapeutic product. There are a number of other products coming down the pike.

What you are going to hear about tomorrow is the first genetically engineered animal intended for food use. What we want to be able to tell you is that these animals are here and that we have developed a rigorous process that has undergone notice and comment period already to regulate them.

(Slide)

So animals and humans -- this is a cave painting from the caves in Lescaux, France. It was painted probably about 15,000 to 10,000 years before the current era. The painting, interestingly enough, is made from charcoal in the blood of animals themselves, so the ochre colors that you tend to see is often mixed up blood of animals themselves representing the animals, which is kind of an interesting commentary, I think. But here we have people already dealing with animals.

(Slide)

So, how did we start domesticating animals?

Well, about 13,000 years before the Common Era, wolves began to become domesticated into dogs somewhere in China. Goats began to be domesticated about 10,000 years before the Common Era in Asia Minor. Swine became domesticated next, again in Eurasia, about 8,000 years before the Common Era. Cattle are -- were domesticated from the now extinct auroch in areas that are now Anatolia, or Turkey. And the poultry from which we derive Colonel Sanders these days was first domesticated in Southeast Asia from jungle fowl. So we have been working with animals for quite a long time. About 1,000 years ago, in various places, China and in some places in the Mayan kingdoms, fish began to be domesticated and people started to do fish farming with carp.

(Slide)

So what are -- have human and animal interactions been all about?

Well, we get food from animals -- we get meat, milk, eggs, blood, rennet. It used to be before chymosin, which was the first recombinant protein that was approved by the Agency, rennet was extracted from the stomachs of calves and used to make cheese.

We have used animals for dray purposes, to -- for locomotion and mechanical power. Companionship and rodent

controls. For those of you who have as many cats as I do, you can worry about how they are sloughing off on the job because there are four-legged animals outside that shouldn't be there.

Protection and herding. We have all known about dogs and the role that they can play, but llamas have been used for protection in South America.

We get fiber from animals when they are alive and both when they are deceased.

We get fuel from animals, from their dung. Even today, people often burn dung from buffalo for fuel, and their bones when they are deceased.

And shelter. We have used hides and bones to build shelter. Some of the early caves in Lescaux, for example, have holes in the floors of the stone where mastodon bones would have gone and hides would have been stretched to build a little tent inside the caves.

So we have been working with animals for a very, very long time.

(Slide)

So what is different now? What is different about our interactions with animals?

Well, we have spent a fair amount of time, last couple of thousand years, developing improvements in isolating and characterizing naturally occurring desirable traits by using chromosomal mapping, trial and error method initially,

but the more we understood about genetics, the more we understood that we might be able to map locations on chromosomes that are associated with particular traits and use that as a way to help develop breeding programs.

We have accelerated the introduction of desirable traits, of naturally occurring desirable traits, into herds by assisted reproductive technologies that range from artificial insemination to nuclear transfer.

And finally, we have begun to introduce new traits into animals by using the tools of modern biotechnology. Some people refer to this as “genetic engineering.”

(Slide)

So how do we do this? This is -- by the way, I believe this is -- is this Jewel or Gem?

MR. : Gem.

DR. RUDENKO: Gem? Okay. This is Gem, who is our Jersey cow who was developed in Beltsville, just up the road, by Bob Wall’s group and I believe Kevin, you were also involved in that. Jewel -- Gem? Do you know?

MR. : Gem.

DR. RUDENKO: Gem. Gem -- hi, Gem -- has a gene expressed in her mammary gland that makes her resistant to mastitis.

(Slide)

So, assisted reproductive technologies, as I

mentioned before, go all the way from selective breeding to animal cloning and they increase the likelihood of getting desired genetic outcomes for naturally occurring traits.

These techniques differ from genetic engineering, and here I would like to introduce you to Petunia, who is our genetically engineered pig. Petunia has a gene that has been introduced into her and she has a trait that she is expressing. The trait is the star. We don't really know what the trait is because Petunia is a generic pig for us, but Petunia can either have that trait introduced as a non-heritable construct or as a heritable construct, and Guidance 187, which we have written and which has undergone the notice/comment process and that Ms. Epstein will be telling you about, addresses particularly animals with heritable constructs.

(Slide)

So what are the differences between the two tool sets that we have?

Well, the goal of each method is different. If we are talking about assisted reproduction -- assisted reproductive technology, what we are talking about is accelerating the introduction of naturally occurring desirable traits into herds, okay? We want to move the quality of the herd to the right, to the good side, as quickly as possible.

Genetic engineering, on the other hand, introduces a

specific trait that may or may not exist in that species or in that animal for purposes of getting a new trait, or an enhanced trait, into that animal and then that animal can be reproduced via our assisted reproductive technologies to accelerate the introduction of that trait into a particular herd.

(Slide)

So, let us -- we have got Petunia back here -- let us talk about how genetic engineering can be used for both agricultural purposes and for biomedical purposes.

In point of fact, we have got all these technologies -- genetic engineering is not the be-all and end-all; genetic engineering is not a panacea for anything; it is simply a tool in the 21st century toolbox. Included in that tool are -- is everything from breeding to marker-assisted breeding to doing genome-wide studies to genomics, perdiomics, metabolomics. All this other stuff that has been developed in the last 15 or 20 years aids us in trying to identify the kinds of traits that we think would serve animals and humans best.

Now, how do those traits aid us?

Well, in the agricultural sector, we can get animals that have increased meat or milk quality or -- and/or composition, we can have increased productivity. But more importantly, more importantly than the traits that are going to be suiting us, are the traits that can suit the animals and

help the animals' health and welfare, including better confirmation, disease resistance, hardiness, changes in fertility and fecundity, developing environmental tolerance in conditions of heat and drought, and leaving a smaller environmental footprint.

In the biomedical field, animals -- genetically engineered animals can be used as models of human disease. We have been hearing about mice and rats being used as models of human diseases. We also hear about a lot of drugs failing in Phase II clinical trials. That may be because mice and rats are not the appropriate models for human; the qualitative differences are too extreme. So perhaps there are other animals that can serve as better models for human disease.

We have animals that can be used as sources of xenotransplantation, cells, tissues and organs. There is an enormous need for transplanted organs. At the moment, I believe there are 98,000 people waiting on the kidney transplant list.

And genetically engineered animals can make biopharmaceuticals. Non-genetically engineered animals have been making biopharmaceuticals since the beginning of time. We get growth hormones in them. Insulin -- until Humulin, the recombinant form of insulin, was approved by the Agency. All of the insulin that people used came from cattle and pigs. Likewise, heparin. You all have heard about the heparin scare

that we had. That all came from pigs as well.

And then we can also develop high value products. There are people at the University of Wyoming who are developing goats that have spider silk in their milk. Why would you want to have spider silk in the milk of a goat? Well, that material can be spun so thinly and so finely that it can be used as ballistic protection devices.

So these -- this is the range of kinds of materials and products that can come out of genetically engineered animals.

And on the left hand side of the page are all the tools that can go into -- you noticed I said “genetically modified animals.” All of these traits, all of these techniques, can be used to modify them. Only some of those techniques are genetic engineering.

(Slide)

And what we are going to talk to you about today is how that started. All of you know that the principles of heredity were first described by Gregor Mendel in 1865, who demonstrated that there were indeed some traits that could be predictively passed from parent to offspring.

(Slide)

Martha Chase and Alfred Hershey -- I don’t think he is the “chocolate Hersey” at all -- first demonstrated to us that DNA was indeed the material that transferred the genetic

information. Those of you who are students of microbiology or genetics will remember the experiments in which they infected bacteria with bacteriophage and then lysed the bacteriophage off the bacteria by putting things in a Waring blender. Waring blenders were really top-notch high technology tools that were used in the labs in 1950.

And what they have discovered is, depending on when you lysed the bacteriophage off the bacteria, you either got or did not get in some DNA, and depending on whether or not the DNA got into the bacterium, you actually transferred genetic material as well, genetic information.

The structure of the genetic code was determined not just by Watson and Crick but by Rosalind Franklin as well in 1953. We have to stick up for our sisters here.

(Slide)

And my favorite line in any scientific publication is the first line of the next to the last paragraph of the paper that says, “It has not escaped our attention” -- understatement of the year -- “that the structure of DNA also provides a mechanism for which it can replicate itself.”

(Slide)

By 1972, we begin to enter the age of molecular biology. For those people who think molecular biology was developed yesterday, 1972 was a long time ago, right?

Paul Berg and Herb Boyer did the basic recombinant

bacteria experiments. The first transgenic animal was actually made in 1974, quite a long time ago. In 1982, Richard Palmiter made a couple of transgenic mice that had thymidine kinase gene in them and the growth hormone gene in them as well.

By 1982, we were beginning to develop genetically engineered food crops, and the first food crop that came to the Agency was the Calgene Flavr Savr Tomato, okay?

(Slide)

So how do we make a genetically engineered animal?

As I have said before, we use recombinant DNA techniques. Our basic construct has essentially three parts to it. It has a traffic signal that tells the cell's machinery that it is time to start making the stuff that we are putting in here right now. That piece is called a "promoter." It has the coding sequence or the gene of interest -- that is the stuff you want to make. And it has something called the terminator -- it has nothing to do with the Governor of California. It just tells the rest of the machinery to stop transcribing here.

So a good construct, a well constructed construct, has a good promoter. That promoter operates either in a specific tissue or generally; you can choose promoters that are on all the time, that only are on some of the time, that are only on in some tissues, that are on in all tissues,

various kinds of promoters. You can pick one of those out of the box.

You can get a coding sequence that can come in or out of a box. Sometimes, those knock genes out, but often we are thinking about positively expressed traits. And the terminator says, “Stop here.” And there is a really good reason why terminators are used, and that is so you don’t get read-through of the coding sequence and start making novel proteins that you are not expecting to make, okay?

So, moving forward.

(Slide)

So how do we actually get to making an animal?

We take our construct, and Jeff will tell you a whole lot more about how you make constructs, we introduce it into a chromosome. It ends up at a particular site, or sites, in the chromosome. We call that a “locus.” We call that “insertion of end-of-transformation event.”

Eventually, if it gets in appropriately, the cell recognizes it, messenger rDNA is produced for a positively expressed trait, and then you finally get the protein of interest out at the animal at the end.

(Slide)

So what we would like to do -- this is another one of the goats who -- that expresses antithrombin in its milk.

(Slide)

So what we want to do, if you want to get a particular phenotypic trait out, is we design the rDNA construct to be the way we wanted it. There you see it. It has got a promoter, a coding sequence, and a terminator.

We introduce it into an egg. In this particular case, I am just using mice to describe this process. This is a Particular Matters case so I don't want to influence you one way or the other, but we are just using mice as an example, and this is only one way that you can make a genetically engineered animal.

You can super-ovulate a female animal, get an almost-mature oocyte, micro-inject that oocyte, or you can fertilize the oocyte so you have a fertilized egg and then micro-inject that. Introduce that fertilized egg into a synchronized animal. Those fertilized eggs will turn into embryos and fetuses. I think -- yes, I am supposed to be doing this, right, Eric? Yes -- sorry.

And then we get genetically engineered -- we get a bunch of animals out. They may or may not be genetically engineered. You need to screen them to see if they have the gene of interest, and if they have the gene of interest and express the product, the trait that you are interested in, then you can start breeding up the food stock.

So, I am finished -- I am finished -- you can wake up again.

(Laughter)

DR. RUDENKO: So, here we go. Our first conclusion is that genetic engineering is not a brand new science. It is pretty well studied. It has been around for much longer than most of us know, probably much longer than most of you guys have been around.

Genetically engineered animals are here to stay. They are a reality.

We have developed a rigorous process to regulate them, and the rest of the group is here to tell you about that.

Thank you very much for your time.

DR. DUNHAM: Thank you very much, Larisa. I appreciate that.

We are now going to move on and we are going to have a presentation now on the National Environmental Policy Act.

MR. : (Away from microphone)

DR. DUNHAM: No, we are not. Let me back that one up. I apologize. I am moving too fast. That is my problem. I am going to slow down.

Now, we are going to have a presentation by Laura Epstein, who is our Regulatory Counsel to FDA in the Office of Chief Counsel, and she is going to talk about the new animal drug approval process as it applies to genetically engineered animals. Laura? Thank you.

MS. EPSTEIN: Thank you. I guess a little apology, just like Larisa did, at the beginning. I know that many of you already know a lot, or everything, that I am going to talk about. But for those of you who don't, hopefully this will give you just some sort of basic familiarity with the law as it pertains to new animal drugs and as it is applied to genetically engineered animals.

(Slide)

So, regulation of genetically engineered animals -- what is it that we are regulating? That will be the first thing that I am talking about, and it may sound straightforward but it actually is a subject that engenders a great deal of confusion and I will tell you why that is, and how it is that FDA is regulating genetically engineered animals.

And again, you have probably heard some of that, but give little bit of specifics about that.

And then how it actually applies in practice. We will talk about how new animal drugs are regulated, but then, how is it going to apply?

(Slide)

So, what is it exactly that FDA is regulating? Is it an animal? Is it a drug? Is it a food?

And the answer is: Yes.

(Laughter)

MS. EPSTEIN: There are aspects of all of these that are being regulated, and that is why it gets a little confusing when we talk about what exactly is it that is the article that is the subject of regulation?

And to some extent, the different articles are subject to different processes and different laws, so that can make it even more confusing. So I am not going to fully answer this question right now.

(Slide)

I will come back to answer it after talking a little bit about: What is GE animal?

Well, you have already heard quite a lot about what that is from Larisa, but what it says in the Guidance document that we issued -- I can’t remember the exact date but -- what was it?

MS. : 2009.

MS. EPSTEIN: 2009, in the beginning of the year, in January -- that document defined a genetically engineered animal as “animals modified by rDNA techniques, including the entire lineage of animals that contain the modification.”

The Guidance document did point out that those modifications can be heritable or they may not be heritable but that Guidance document was only going to address the

heritable traits, and that is what I am going to be talking about right now as well, even though that it is possible that you could have some that are not heritable.

So, when you -- the GE animals that have these heritable modifications will contain that rDNA construct in their cells. Larisa gave you a very good illustration of exactly how it works, that the rDNA construct is inserted and imparts these new traits to the animal. And it could be any number of different traits. And I apologize -- a word kind of [fell off] of this slide; I think that was supposed to be "protein."

The new trait might be gaining of a function, so it could be expression of a protein and with -- Larisa talked about some of the things that it might be, which, you know, increased growth or it might be expression of a human drug in its milk, or any number of things, or loss of a function. And it is this rDNA construct that we are going to be discussing and that the Committee will be deliberating about, which is a drug.

(Slide)

Well, why is this construct a drug?

It doesn't seem to make intuitive sense, but in fact, the definition of a drug in the Federal Food, Drug and Cosmetic Act includes -- it is sort of a long definition, so I won't read the whole thing, but the relevant part is that it

includes an “article intended to affect the structure or any function of the body of animals.” And we have just learned that that is exactly what the rDNA construct in that animal is intended to do; it is intended to impart new traits.

So, therefore, that rDNA construct meets the definition of a drug and is subject to FDA regulation under the drug laws and rules.

So, going back to what it is we are talking about here. So we start with the rDNA construct and it goes into this animal and you have this transformation event and it -- because we are talking about a heritable construct, each generation of the animal is going to have the construct in it, which is the regulated article in this case. So we can go back and test the second generation, the third generation, many generations thereafter, and still find that article in the animal. It is still going to be present.

And then that animal in turn may produce other products, and it may be that those are food products. It may be that, like the goat that was referenced, it is producing a human or perhaps animal drug. Or it may be something that possibly might not be regulated at all by FDA.

Larisa referenced the spider silk in the milks which, you know, just -- I am sure many of you have read various articles about it, that, you know, this could be an industrial material used to make canoes and bullet-proof vests

and things like that that ordinarily FDA wouldn't regulate.

So there is a part of it that FDA is regulating, which is this construct which falls into the new animal drug scheme and then there may be this other product that is being produced by the animal which could be regulated by FDA under another scheme, so you would have the food laws that might apply to food, you would have perhaps human drug laws that might apply to a human drug, or in the case of a product that is not regulated by FDA, then the product goes on its way and perhaps another Agency may or may not regulate that.

(Slide)

So how does FDA regulate genetically engineered animals?

(Slide)

Well, in general, a new animal drug has to have an approved New Animal Drug Application before it goes on the market. And, like Larissa, I have to say "in general," because there are exceptions to it.

But the new animal drug in this case would apply to all the genetically engineered animals that contain that same rDNA construct from the transformation event which Larissa described. All of those would be the same new animal drug.

Now, you could take the same rDNA construct and have a different transformation event, so there may be multiple transformation events as the animal is being developed in

trying to develop the line that really is going to be the one that works. Each of those different transformation events would be subject to a different New Animal Drug Application, so where we are considering one New Animal Drug Application, we are talking about that single transformation event and the animals that are part of that lineage.

And the same requirements that are going to apply for any new animal drug, because we are talking about the same new animal drug legal scheme, are going to apply with respect to this new animal drug that covers all of the animals that come from this same transformation event for the rDNA construct.

(Slide)

So as I said, there are some exceptions, but in general, you do have to have an approved New Animal Drug Application, the only exceptions being if it is -- if you have an INAD, which is an Investigational New Animal Drug exemption, which is what you have while the drug is being studied, or you are either approved or you get conditionally approved or indexed. The conditionally approved and indexed aren't really relevant for purposes of our discussion because indexing only applies to non-food animals. In any case, we are not talking about a conditional approval or if you have off-label use that complies with statutory and regulatory requirements, and again, we are not talking about that here.

It would be pretty hard to have off-label use of this particular type of drug that you are talking -- going to be talking about tomorrow.

(Slide)

The other exception, which is covered in the Guidance document on -- and is not, again, relevant for this, but just so that you know what it is -- since I am sure that you have read through the Guidance document -- are those cases where the Agency does have jurisdiction but has stated that it intends to exercise enforcement discretion. So, you know, those are just certain discrete categories of animals, like non-food animals that are regulated by their agencies or lab animals that are in contained and controlled conditions or certain very specific examples of non-food animals that are evaluated on a case by case basis.

(Slide)

I am not going to go into great detail about what the requirements are. You are going to hear a little bit later about how the Guidance document interprets the rules to apply to genetically engineered animals.

But, in general, the purpose of that Guidance document was to say, you know, “Here is what all the laws and regulations are that apply to new animal drugs, and here is how they are interpreted to apply in this particular circumstance.” And, you know, those are the types of Guidance

documents that the Agency issues all the time because every specific type of product has its own issues that call out for a particular interpretation of the general rules, and this is no different.

But the general requirements under Section 512(b) of the Federal Food, Drug and Cosmetic Act which govern New Animal Drug Applications and what has to be submitted in those applications and what the standard is for approval, that applies. And all the regulations in Part 514 that apply to new animal drugs also apply in this case as well, and similarly -- and I will briefly go over that, but you are going to hear a great deal of detail about NEPA; NEPA does apply as well, the National Environmental Policy Act.

(Slide)

So what are the standards for approval?

With a new animal drug, you are talking about multiple standards, not just one which you might have with, for example, a human drug.

So, you know that the drug has to be safe. There are two pieces to the safety.

One is that it has to be safe to the target animal itself, and so that is sort of similar to the human drug piece of it where you are just looking at, is it safe to the person who is taking that drug? So, the animal that is getting the drug, is it safe to them?

And then there is the food safety piece. So, is it safe to humans that are going to consume food derived from the animal treated with the drug? And for that, the standard is "reasonable certainty of no harm," which is a very high standard. It is a high bar to be.

And lastly, there is effectiveness. There must be substantial evidence that the drug has the effect that it is represented to have.

(Slide)

And how is that now going to apply here?

(Slide)

Well, the target animal's safety: Is the rDNA construct safe to this particular salmon?

That is taking that legal standard and applying it here, that is what it means. Are there any safety issues? Can we make a finding that it is safe to the target animal, i.e., the salmon?

Food safety -- so here, we are talking about: When we look whether or not this is safe, we use as the baseline other salmon, because there may be reasons why, and for particular people, that any salmon is not going to be safe for them. For example, we know that salmon, like most fish, are highly allergenic for certain people. So, if you are already allergic to any salmon, you are probably going to be allergic to these salmon, too, so you start with that baseline.

And then look at: Are there potential harms to human health that don't exist with other salmon and that do exist here? Or, are the existing harms, for example, the allergenicity, greater for AquAdvantage salmon than they would be for other salmon?

And then, lastly, there is effectiveness, which is fairly straightforward. You look at the claim that the sponsor is making that these salmon grow faster and ask: Is there substantial evidence that, in fact, these salmon actually do grow faster?

(Slide)

Then, there is also -- as we said, there is the National Environmental Policy Act and there is a separate standard for that. So, for every major Federal action significantly affecting the quality of the human environment, NEPA requires a detailed statement on the environmental impact of that action.

And, you know, major Federal action is something that confuses people a lot. It is not very clear what that means, but for our purposes, what we do know it means is that approval of a new animal drug is a major Federal action.

So, NEPA applies with respect to all approvals of new animal drugs, which means that FDA has to determine whether or not, if the New Animal Drug Application were approved, would that have a significant effect on the quality

of the human environment?

Then -- so we do this analysis and determine whether or not there are significant impacts or, you know, if there are impacts, are those impacts adequately mitigated?

And if so, then the Agency issues what is my favorite acronym, a FONSI. A FONSI is a Finding of No Significant Impact and Eric will put on his leather jacket to do -- there is a FONSI and that is the procedure! No -- sorry. So that would be one finding.

On the other hand, if there are significant impacts after doing this analysis, then the Agency has to prepare an Environmental Impact Statement which is, you know, further review of the environmental impact.

(Slide)

So, what are you, the Committee members, going to be looking at?

We are talking, again, about the same standards for approval that the Agency has.

So, of the questions that were posed to the Committee, do the data and information demonstrate that the rDNA construct is safe to AquAdvantage salmon? That is the target animal safety standard that we just talked about.

Do the data and information demonstrate that there is a reasonably certainty of no harm from consumption of foods derived from AquAdvantage salmon? Again, that is the food

safety standard.

So, we start with target animal and then the food safety standard, and we just talked about sort of what those questions are going to be for food safety. And you will get a whole lot more detailed information later about that.

Do the data indicate that AquAdvantage salmon grow faster than their conventional counterparts? There is the effectiveness.

And those are the three approval question standards under the Federal Food, Drug and Cosmetic Act. And then this fourth one is the NEPA standard, under a different statute, obviously, NEPA: Are any potential environmental impacts from the salmon production adequately mitigated by AquaBounty Technologies' proposed conditions of use?

So, again, this is the question of whether there are any significant impacts. If there are, are there mitigation measures in place such that you can reach the Finding of No Significant Impact, the FONSI? Or is an Environmental Impact Statement required?

(Slide)

There are a lot of issues that are of great concern to many people about genetically engineered animals in general and the salmon that you are going to be looking at in particular, but not all of those issues are within the scope of these standards that we just talked about.

So, there has been a lot of discussion in the press about these larger ethical and societal issues. A lot of people feel that it is simply wrong to create these types of animals, that the government shouldn't permit this. So those -- while there may be valid concerns like that, what the Committee is going to be looking at are the legal standards for approval, and those types of issues that are outside the scope of it -- again, while they may be valid, they don't fall within those standards for approval.

And then, similarly, you know, if there is popular opinion that is not based on the type of data that we are looking at here -- now, again, I would say some people might say, "Well, it is data if you do a study and find, you know, X-percent of people just don't like this," you know, we are talking about this sort of scientific data that would show whether or not it is safe and effective.

And, lastly, and this is an issue that is of importance to FDA -- it is just not the issue that we are looking at at this meeting, which is the labeling of food products derived from AquAdvantage salmon.

And the reason for that is there are two types of labeling. There is labeling of a drug product. There is labeling of food that is derived from an animal. So there will be labeling that accompanies animals that have the rDNA construct that would be considered to be drug labeling, but

when you are buying some sort of food product that is derived from the animal, that is a separate issue and that will be the subject of the Public Meeting on Tuesday.

(Slide)

So what will the process be?

The Committee is going to consider the questions that we just discussed and then, based on the data and the comments received and your deliberations, you will make recommendations to the Agency on those questions.

Then, under NEPA, FDA will consider the Committee's recommendations.

There will also be public comment. The draft EA -- environmental assessment -- will be posted and there will be public comment on that, and the Agency will consider that as well.

And -- well, I skipped ahead of myself. The -- when the EA is made available for public comment, there will be a Notice in the ***Federal Register***. And then we consider the environmental assessment in light of all of that input and determine whether or not there is a significant impact.

Then, under the Federal Food, Drug and Cosmetic Act, the Agency will consider the entire record, including your deliberations and recommendations, any public comment that is made at this meeting, and decide whether or not to approve the New Animal Drug Application.

So, hopefully that was a helpful sort of overview. You are going to hear a lot more specifics about how those laws have been interpreted in the Guidance document over the course of other people's presentations and also right now a lot more detail about NEPA and how it applies. Thank you.

DR. DUNHAM: Well, thank you very much, Laura. I hope you all found that very, very helpful. I really do appreciate that.

Now we shall proceed. And Dr. Eric Silberhorn will be talking about the National Environmental Policy Act, or NEPA. Eric is an environmental scientist and training with expertise in fish biology, toxicology and environmental risk assessment. He was a primary reviewer of the information on the phenotypic characterization and environmental safety assessment of AquAdvantage salmon. Eric? Thank you very much.

National Environmental Policy Act (NEPA)

by Eric Silberhorn, Ph.D., DABT

DR. SILBERHORN: Good afternoon. So, Laura gave you a little introduction to some of the terminology. I am going to take that a little bit further and talk about -- give you a little more background on NEPA, the National Environmental Policy Act, and how we implement it, and some of the unique aspects of it.

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So again, I am going to cover some background information, a little bit about the law and our implementing regulations, some terms and definitions which come into play in interpretation in our decision making, how some of the environmental documents that are prepared and the scope and the breadth of those, FDA's responsibilities in this whole process and how the public can in certain points participate in this process.

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So, as Laura said, the Federal Food, Drug and Cosmetic Act has its own standard and new drugs must be found to be safe and effective.

Under NEPA, the National Environmental Policy Act, there is a requirement for FDA to review, conduct environmental review, of FDA-regulated articles to determine if the use and disposal of those articles would have a significant effect on the human environment.

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So, NEPA was passed about the same time that the Environmental Protection Agency was formed, back in 1969, and it applies not just to FDA by any means but to all Federal agencies and requires them to review and be informed of the potential environmental impacts of any actions that they may take, or any major actions they may take. And that really has very wide breadth and it affects all agencies.

So the goal of NEPA was to insure that there wasn't -- to maintain environmental quality and insure there was no degradation of environmental quality. And back -- if some of you may remember back that far -- that was a very important concern, and still remains to be at this time.

The other thing that NEPA did was it formed the Council on Environmental Quality, which is usually referred to as CEQ, and that is an agency that sits in the White House in the Executive Committee and oversees NEPA requirements and NEPA implementation through all the Federal agencies.

And the thing about NEPA was it was specifically made to encourage public disclosure and include the public in the decision making process to the extent possible but to -- that that, our environmental decisions. And moving forward on environmental matters would be science-based and based on expert opinion and expert comment.

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So, NEPA has its own regulations, or CEQ has these regulations, that are codified in Part 40 of the Federal Code of Federal Regulations, Part 1500. They are very wide-ranging, but among the things that they talk about and that FDA has also picked up in its own regulations are things such as categorical exclusions, which I am not going to get into too much today, but environmental assessments and Environmental Impact Statement.

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So -- but FDA has its own regulations that -- where we have codified -- or our own implementation of NEPA. And because FDA has unique issues because of confidentiality and trade secrets, our process -- you know, as all agencies can have unique aspects of their implementation of NEPA because of these kind of issues.

So this is the listing. I am going to go through, sort of highlight some of the important parts of these different sub-parts that apply and I think that people need to be aware of.

But they include things like: What actions require environmental assessments and what type of environmental assessments or Environmental Impact Statements? How we prepare documents. How are they reviewed? How does the public participate in the process? An important is this Subpart F, at the bottom there, that it talks about Executive Order 12114, which is Environmental Effects Abroad, and that is an Executive Order that has been codified in our regulation.

(Slide)

So what does FDA do under NEPA?

Well, the most common thing we do, and this is the part of my job every day, is that we review categorical exclusions. I am not going to get into a lot of what a

categorical exclusion is, but it is essentially a means a shortcut environmental review. That doesn't apply to GE animals and so we are really not going to talk about it.

But the main thing -- the other main thing we do is we review and help direct preparation of environmental assessment documents and review data submitted by sponsors and applicants and then make decisions whether we need additional data or additional assessment, or whether we can make this FONSI, as Laura has introduced, this term "the Finding of No Significant Impact," whether we can make a FONSI or whether we determine that we need to prepare an Environmental Impact Statement. And if we do have to prepare an Environmental Impact Statement, there is a decision document associated with that which is called a Record of Decision, or a ROD.

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So this is sort of a -- the flow-through for that process.

So, starting with a regulated article which could be, you know, a food, drug, a lot of different things in our case. In our case, this could be a GE animal that would be subject to a New Animal Drug Application. If it meets a criteria for a categorical exclusion, then the environmental review would stop at that point, but as I said, that doesn't apply for GE animals.

So the next step would be to move to environmental

assessment, and then from there, there are really two different directions you can go.

If the Agency makes a determination that the approval action that may result may significantly affect the human environment, then we would be required to prepare an Environmental Impact Statement, and associated with that, a Record of Decision.

If we determine there is no significant impacts from the approval decision, then we would prepare a Finding of No Significant Impact, which is a -- again, it is a document, a decision document, that outlines our decision and the basis for our decision and the data which we considered in making that decision.

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So, most -- a lot -- you know, we have got specific requirements about when we do environmental assessments. It is codified again here, in 21 CFR, Part 25. It includes New Animal Drug Applications, abbreviated applications which are things like generic drug applications, supplements to those, actions on INADs, which is investigational use of drugs, requires environmental review. And all these things occur unless there is a categorical exclusion that applies.

And again, as I said, categorical exclusions do not apply for GE animals and aren't expected to for the near future, so that is not an option.

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So, are there any actions that normally would require an Environmental Impact Statement?

And the reason this is put in here is because for some agencies there are certain actions that they automatically prepare an Environmental Impact Statement for. But for FDA, we have determined, based on history of use and that kind of thing, that there are no actions that normally require preparation of Environmental Impact Statements.

So we don’t go that route; we always start with an environmental assessment. So -- but an Environmental Impact Statement would be prepared if we had information or data that led to a finding, after a review of this information, that the proposed action may significantly affect the quality of the human environment. So that is the standard that we have to determine, or we have to evaluate against.

(Slide)

So, under the CEQ regulations, which are referred to in our own FDA NEPA regulations, the term “effects” is defined, and it is important to know what does that mean, because that essentially bounds what we need to consider in our environmental assessment.

It can include direct effects -- things that occur at the same time and place as the action, or it can include things that are indirect effects, but only those things that

are reasonably foreseeable, so that means we can't consider the universe of possibilities; we really only can consider those things that are reasonably foreseeable.

Generally, the effects, and particularly at FDA and, you know, at EPA and those kind of agencies that deal with things that go out in the environment, we are really worried about ecological effects, but there is a requirement that the effects could include, if relevant, things such as economic and social and health effects.

Now, health effects are already evaluated by -- as part of our human food safety, so we don't normally look at that kind of thing. But it is really important to note that the economic and social effects by themselves will not require preparation of an Environmental Impact Statement.

So, in other words, if we have determined that we don't believe there are any ecological effects, we wouldn't go on to prepare an Environmental Impact Statement just because there might be economic or social impacts, or effects.

And under NEPA -- you may hear me interchanging the term "effects" and "impacts" and that is because under NEPA those are equivalent terms so they are used interchangeably --

(Slide)

The other important term is "significant" because we say "significant effects," and that is the standard. So what does "significant" mean?

Well, it has to be considered both in terms of context and intensity. So, the intensity, there are a number of factors and I haven't even listed these all, but these are again in the CEQ regulations in Part 40 CFR. It talks about these things that you need to consider. There are no bright lines for these things, but they are things that you need to think about when you are trying to make that determination of whether the effect is significant or not.

And those things can include: Whether the effects are on public health or safety, whether they are highly controversial, whether there are highly uncertain or unknown risks that might come into play, or whether the action might be setting a precedent for future actions. So -- and also, whether the effects could be on threatened and endangered species.

(Slide)

So, what is an environmental assessment?

It is actually supposed to be a concise, balanced, objective document. I say "concise" because sometimes they are not always so concise. But it allows -- it is actually a -- it is a document prepared to communicate in, you know, science to the public eventually so that the Agency's decision, the decision is going to be a FONSI, usually, from an EA, but why and how did the Agency come to make that decision?

So it is meant to be not -- although they are very technical documents but they should be able to be understood by the public. And again, they have to provide a sufficient analysis and evidence for the Agency to determine whether there should be a FONSI or whether there should be an EIS.

So, there is a whole -- there are, you know, things that should be included, but typically ours are set up on a risk-based approach so we can have exposure and effects kind of things. But some of the things that are required are the need for the proposal, if there are potential alternatives. Now, for new drugs, there usually aren't real alternatives except for mitigating factors that could be put into labeling and that kind of thing; the alternative is approval or not approval and that is usually the major alternatives.

And if there are environmental impacts, obviously they are discussed, and if there is a consultation, that is -- consultation with other agencies -- that is disclosed. Ultimately, if there are -- if it is concluded that there might be environmental impacts, then they need to -- alternative, reasonable alternatives need to be discussed.

(Slide)

So, what are FDA's responsibilities for the EA?

Well, the FDA is responsible for the EA. We are responsible for the total scope and content of the EA.

But in reality what happens most of the time is that

the applicant, or the sponsor, actually prepares the EA under our direction and, you know, this is -- can be a very long and involved process, take -- I can think of some that have taken over 10 years to get to the point where they were acceptable to the Agency to be a public document and make a Finding of No Significant Impact, or making a decision.

So, it is also important to note that FDA can require information be put into an EA even if it is prepared by a sponsor, so we can always add information or we could add information into FONSIs to supplement what is in the environmental assessment if we have additional information that is available to us from other sources.

So, normally the EAs and -- because our -- normally, the EA and the FONSI are made public after approval decision is made so there is a Notice in the ***Federal Register*** and it becomes available through our public docket. But we also at the Center for Veterinary Medicine usually make our EAs and FONSIs available on our website also for new animal drugs.

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But -- so that would be on a post-approval basis.

But there are -- as shown here in our regulations, there are some potentials to have pre-approval public participation and that is for a certain limited number of actions, and I -- to be honest with you, I can't think of one that this has ever happened before, but the Agency may make

the FONSI and the EA available for public review for 30 days before the Agency makes its final determination whether to prepare an EIS and it is also important before the action may actually occur, so in other words, before an approval could occur.

So this procedure is followed when the proposed action is, or closely follows one that normally requires an EIS, which I have just told you we don't have any standard conditions where that is the case, or where one -- the proposed action is one without precedent.

(Slide)

So the other thing that is important to note, and this has been codified in our 21 CFR regulations, environmental impact regulations, is that all Federal agencies must consider the potential impacts abroad, the environmental effects of actions that take place abroad.

So, as we will talk about tomorrow, this comes into play, but that includes consideration of the effects on the global commons. The global commons are things such as the oceans and the upper atmosphere, places that are outside the jurisdiction of any particular nation, so in other words, no one actually has control of them directly, effects on foreign nations that aren't participating in the action, so that is sort of third parties that might be injured inadvertently and also if there are potential effects on resources of global

importance. So those can be things like minerals or ecological resources, that kind of thing.

(Slide)

So, in summary, the environmental assessment is required for a New Animal Drug Application for a GE animal. Based on the EA then, the Agency would make a determination whether to prepare a Finding of No Significant Impact, a FONSI, or whether an Environmental Impact Statement is needed.

And if the action is one without precedent, then the EA and FONSI will be made available for public comment before the Agency makes its determination, or decision. And that -- when I say “decision” there, it would mean the decision whether to actually prepare an EIS or not and the decision of whether to approve the drug, both of those. And Agency actions that must require, or must consider, environmental effects abroad, including the effects on the global commons, other foreign nations, and resources of global importance. Thank you.

DR. DUNHAM: Thank you very much, Eric. Well, I hope you have really enjoyed the first set of presentations which have really been meant to try to help educate and have you understand what is behind all the reviews that we are going to be talking about in more detail tomorrow of the specific project.

What we can do right now is take a break, and

because we are ahead of schedule, if you are amenable, we could take a 15-minute break, be back here at 2:45, and commence and hopefully get you out to enjoy the rest of a beautiful afternoon.

The VMAC will be asked questions, and if anybody in the audience has questions, you can write those down on the cards and we will take those when the question and answer portion takes place this afternoon.

So if that is okay, I want to thank all of our speakers so far, and let us take a 15-minute break and be back at 2:45. Thank you.

(Whereupon, the Committee took a break from 2:27 to 2:50 p.m.)

DR. DUNHAM: All right, to continue with a very good educational afternoon, we are going to move forward now and we are going to bring Dr. Rudenko back to the podium and she is going to do an overview with the rest of the team for the afternoon on introduction to the regulation of GE animals at FDA.

Following that, we will have questions from the VMAC Committee first, and after that, we will receive any questions from the audience and there will be some cards being passed around so that you can write your questions down and then we will address them.

So, with no further ado, let us start the afternoon

session. Thank you. Dr. Rudenko?

Introduction to the Regulation of GE Animals at FDA

by Larisa Rudenko, Ph.D., DABT

DR. RUDENKO: Hi, I am back. Did you miss me?

Before I start, there is a point that we would like to clarify regarding the announcement of what exactly is going to be happening with respect to environment assessment. So I think there is some confusion because there is an environmental assessment that has already been posted and some people think that that is constituting our public comment period. Let me assure you, it is not, okay?

At the conclusion of the Veterinary Medicine Advisory Committee following comments from the VMAC, following comments from the public, we will make a determination as to whether or not we are going to go down the EA route and issue a draft FONSI or the EIS route.

Either one of those decisions will be announced in the ***Federal Register***. Both will have full public comment. There is no limitation on public comment on that particular process.

So I want to make it very, very clear that the release of the EA that was posted right now is for the purposes of letting the VMAC see what we currently have at hand. Everything that was shared with the VMAC is being shared with the public. But that does not constitute the public comment period for the environmental assessment.

Do I need to say it one more time?

(No response)

DR. RUDENKO: Okay. All right. There were some comments that not all of us were close enough to the mike. Is this -- can you hear me in the back?

(Waving of hands)

DR. RUDENKO: --- how about now?

MS. : (Away from microphone)

DR. RUDENKO: Okay. All right. So let me take you through right now what is our methodology.

If we were writing a scientific paper, what we would have done so far would have given you the title, the abstract, and the introduction. And now what we are going to do is tell you about materials and methods.

And tomorrow, you will hear results and some -- and you will provide discussion, all right? If we were using that vernacular.

(Slide)

Okay, so let us talk a little bit about the regulation of genetically engineered animals at FDA just in case you didn’t get it the first three times.

We regulate genetically engineered animals by regulating the rDNA construct that is contained within those animals as an article intended to alter the structure or function of that animal under the Federal Food, Drug and

Cosmetic Act and any major Agency actions that need to be taken are regulated under the National Environmental Policy Act. You should have that by now.

Okay, Guidance 187, which went through a formal notice and comment period and which is posted on our website, describes, clarifies, our legal -- our statutory authority for doing that, translates the regulations that are currently in effect in the ***Federal Register***, into terms that are comprehensible for genetically engineered animals and in the third part offers a set of recommendations for how sponsors may provide data to the Agency to evaluate.

It also gives you an overview of the risk-based approach that we have employed in taking a look at these particular animals.

There are a couple of important take home messages here.

One is that all genetically engineered animals must have pre-market approval prior to being entered into commerce. We won't debate whether or not a biopharmaceutical animal that stays in one place is in commerce or not. We are just going to say that that animal needs a New Animal Drug Application approval. It covers all genetically engineered animals, although there are some exclusions for those animals that are regulated by other entities that are highly contained as in research institutions or for which the risk is so low that

they are covered by enforcement discretion.

This is a soup-to-nuts approach. We start with pre-market approval and go all the way to post-market regulation. You are going to hear about that as the day progresses. And it is a risk-based approach, which means that we attempt to ask specific risk questions and answer those questions on a case by case basis for each individual GE animal rDNA construct products pair, if you will, and each specific transformation in that.

(Slide)

So we believe that each genetically engineered animal and construct event poses unique risks, and because of that, each one requires a specific set of risk questions and a specific set of data and information for the responses.

Why is it that we think that each rDNA construct animal event requires specific -- a separate NADA and separate regulation?

It has to do with insertional mutagenesis and unintended effects that may come as the result of insertional mutagenesis.

When and if homologous recombination becomes the law of the land and everybody can introduce a piece of DNA exactly into a position that they would like to introduce it, we may revisit this.

At the moment, because a piece of DNA generally

incorporates randomly into the genome of the animal, it is impossible to predict whether any adverse outcomes that will occur from that insertion event will be the same if the insertion occurs at different sites.

So for -- in general, for the foreseeable future, while people are randomly introducing pieces of DNA into genomes of animals, we will be regulating them on an event-based basis. There is nothing different about this from the way that we regulate genetically engineered plants, which are also handled on an event-specific basis, okay? So, it is a case-by-case evaluation.

There are specific considerations of the conditions of use.

Because we are operating under the new animal drug provisions of the Act, there must be conditions of use associated with the application, and those are the conditions that bound the risk scenarios that we evaluate.

And finally, unlike USDA or other agencies, we do not do programmatic risk analyses. We do not do a programmatic environmental assessment for all genetically engineered goats. We do not do a programmatic analysis for all cows that contain additional lactoferrin. It is case by case, okay?

(Slide)

So let us talk a little bit -- and I am the coals to

Newcastle lady, so for those of you again who know, and are expert in these things, my apologies, and for those of you who need a refresher course, here it is; we are going to go fast.

What do we mean when we say “risk?” Well, here are the definitions, relationships and standards. I will repeat some of the standards that Laura has introduced to us a little bit earlier.

The first thing we need to talk about is a harm. What is a harm? A harm is an adverse outcome. It is something bad that can happen. If there is a piece of ice on the sidewalk and you slip and fall and break a leg, the harm is the broken leg, okay?

A hazard, on the other hand, is a substance or an activity that has the potential to cause a harm. So, using that same scenario, the ice on the sidewalk is the hazard, okay?

Risk is the conditional probability of an adverse outcome provided that exposure to a receptor has occurred. For those of you who are gene jockeys or molecular biologists, no, it is not that big molecule that a ligand binds to. A receptor in risk parlance is a person or a population experiencing an exposure, okay?

So, a risk, one more time, is the conditional probability of an adverse outcome or a harm provided that exposure has occurred.

So, what does that mean? If there is ice on the sidewalk and it is March and it freezes and thaws and I am walking down the street, the hazard is there. I am the receptor. The harm is that I could break my leg. Am I at risk? Well, it depends on my exposure, right?

If I cross the street and avoid the ice, the harm is still there but there is no risk because there is no exposure, right? If I put on a pair of crampons or sprinkle salt on the ice or I sprinkle sand on the ice, I have mitigated the risk. The exposure still exists, but the risk has been mitigated. And so the probability drops, okay?

So, risk is some function of the outcome and the exposure of the hazard or it is the likelihood of harm given a set of particular exposure conditions that exist.

Now, that is a really important concept. Most people, in using these terms in the vernacular, conflate hazard and risk, or interchange hazard and risk. Just because something has the potential to cause an adverse outcome doesn’t mean it will cause an adverse outcome. It is a conditional probability of an adverse outcome provided that exposure occurs, okay? Please remember that.

And again, as I said, a receptor is an individual or a population experiencing the risk, and as Laura has told you already, safety for the food safety standard is reasonable certainty of no harm.

You can think of safety as being sort of 1 minus risk. It is the space that is not -- given the entire space of risk, the part that has no risk associated with it is safety, for those of you who like to think about spaces and physics.

And the safety standard for animal health is a balance of risk and benefit for the animal health. Is that clear? Have -- I know I have been pounding on this pretty hard, but it is a really important concept. Okay.

(Slide)

So what do we mean by a risk-based evaluation?

This may be the first time many of you are going to be introduced to this particular little pyramid, and it is actually referred to as ziggurat, and the person who is responsible for that name is John Matheson, who is sitting directly opposite me in the blue shirt, looking embarrassed. John, can I make you any more embarrassed?

We came up with this name -- I was calling it sort of a wedding cake -- but it was about the time that things were beginning to hit in Iraq and people had just discovered these new ziggurats, and so John jokingly said to me one day when I brought in this picture, “Oh, it is a ziggurat!” So it became known as Ziggy, for short. But here in this venue we will refer to it as the hierarchical risk-based evaluation.

So, what do we mean here by risk-based? The first

thing we need to do is clearly distinguish between hazard and risk. We need to break the overall determination of safety or risk into separate components or individual steps. We need to ask the appropriate risk questions.

Remember, this is all case by case. It is going to be driven by what the construct is, what the animal is, where the construct is, and what -- whether or not the animal is intended for food, what it is going to do case by case.

And we use something known as a weight of evidence determination for both data and information and to clearly identify uncertainties that may be associated with any of the evaluations that we do.

(Slide)

So, people often talk about intended and unintended effects and direct and indirect risks and they tend to use those interchangeably as well.

This is the part where, if you were in college or a grad school, you would sort of snooze and then go back and take a look at your notes right before the exam, but we are going to go through this systematically because you have got to get this right, all right?

So, direct and indirect effects categorize on the mechanism of action. A direct effect of a phosphatase is to work on something with a phosphate group on it, right? An indirect effect might be that that reaction then causes some

downstream reaction that has been impacted by dephosphorylation or phosphorylation reaction, okay?

Intended and unintended categorize based on the objective of the modification.

So, if your intent is to make the cow that makes only chocolate milk, the intended effect is chocolate milk to come out of a cow. An unintended effect of this might be that the cow's coat is browner, okay? It has nothing to do necessarily with mechanism; it is just an unintended effect.

(Slide)

Okay, so now, hazards and risks again.

So this is the famous pig and the pork chop conundrum. And we start out by saying, "Well, what is the difference between a hazard and a risk? And is the hazard always the same and is the risk always the same?" And the answer is: Depends on who the receptor is.

So, a hazard -- the rDNA construct may produce a potential hazard in rDNA animals. It may pose a health risk to those animals, all right? But, that health risk may or may not be a food consumption risk for the people who are consuming food from the animal.

For example, the health risk may be that pigs have straight tails instead of curly tails, okay? That is not going to affect necessarily the quality of the food or the safety of the food. It is a hazard to the pig but not

necessarily to the human who is consuming the pig, okay?

So, remember whenever you think about hazards and risk, ask: Hazard to whom, risk to what? Hazard to what, risk to whom? A risk always has a receptor in it, okay? It is not a free-standing property.

(Slide)

So, very quickly, and Don Prater will talk to you about this in much more detail, what I have tried to do here is just give you examples of direct adverse effects and intended effects and unintended effects for animal health. And so a direct adverse effect might be considered an adverse outcome from the rDNA construct insertion which, as I said before, could be related to insertional mutagenesis resulting in disruption of important coding regions.

An indirect adverse event could be a perturbation that results from an insertional mutagenesis event or from the gene product being expressed off that rDNA construct which may or may not perturb the animal's physiology. You might, for example, find that you are increasing the rate of the formation of a particular kind of fatty acid and that might be a problem for the animal, okay?

Intended effects are changes that result from rDNA constructs and gene products. They may or may not pose direct or indirect effects on food safety. And unintended effects may be metabolic changes that result from the interaction of

the rDNA product, the expression product of the construct, with the animal's physiology.

So let us think a little bit about a conceptual approach, about how we would think about direct and indirect effects intended for food risks, okay?

(Slide)

This is Molly -- not to be confused with Petunia. Molly is our genetically engineered cow. She may have the same trait as Petunia; it is hard to tell.

And Molly -- when we start thinking about this from the perspective of either the milk or the meat from Molly, the direct effects of the construct insertion to what is the direct risk associated with the insertion of the DNA itself, none -- DNA is grass, okay? So there is no added toxicity, generally recognized as safe. We all eat DNA. Let me know if you eat food that has no DNA in it. I suppose oils have no DNA in them. Yes -- okay, fine; I was wrong. Oils have no DNA in them. But do let me know if there are other foods that have no DNA in them.

Indirect effects are -- again, my favorite point that I keep bringing up, of insertional mutagenesis that may arise. And then we have the gene product, if there is a gene product, from this construct.

The direct effects may be the toxicity that may be associated with the presence of a new protein in a food. That

could be the -- a kind of toxicity that exhibits as a frank adverse outcome or it could be something like allergenicity.

Indirect effects are the metabolic changes that occur such that edible tissue may pose risks.

A really good example of this, so we keep wracking our brains to figure out what a good example of an indirect effect might be. And one might be that you increase the binding affinity of metallothioneins, for example, for certain metals. And so the animal shows no adverse effect even though it is eating in a high selenium soil because the selenium is bound up by the metallothionein. Once you take meat from that animal and cook it and denature the metallothionein, you are actually releasing more metal into the food than you might expect, okay?

So that is an indirect effect that could have resulted from a change in the metallothionein protein. Okay.

(Slide)

So here is our friend, the pyramid, the ziggurat, all over again, and it has got different colors in it. And the colors are important for you to notice: Blue is hazard, yellow is risk determination.

So, the blue steps -- in the blue steps, we define hazards and characterize them. The product definition sort of gives us our baseline to work from, the molecular characterization of the construct and of the construct in the

GE animal lineage. Again, establish a baseline of hazards, whether or not they are there or not.

In the phenotypic characterization, we make the first transition from characterizing hazards in the animal to actually affecting risks for the animal and then characterizing hazards that may pose food consumption risks which are found in the next to the last step before the start.

So, the big safety assessments, the environmental and food safety assessments, cannot be done until you have characterized all of the hazards that have been identified and characterized in the preceding steps.

So this kind of an approach is a -- it may be iterative, it often is iterative, but you cannot get to the last steps until you finish the first steps. And folks will be telling you in great detail about how we did that.

(Slide)

Now, there is something else I want to tell you about that is very different about the way that we as a group -- you were introduced to the group. We don’t often bring a group of reviewers to a Veterinary Medicine Advisory Committee meeting or to any FDA advisory committee meeting. But we did here, for a very important reason. No one reviewer is responsible for making a yea or nay decision on any component of this assessment.

The way that we did this assessment was to pattern

it slightly after an NIH study section. What we did was, with the blessing of the Center directorship, was to say we are no longer going to be bound by administrative units within the Center or within the Agency per se. This is a new technology. It requires all the expertise that we can bring to bear on it, and so we will go out and find the people who have expertise. We don't care whether they are in the Office of New Animal Drug Evaluation, the Office of Research, the Office of Surveillance and Compliance, or the Office of the Commissioner. We are going to go find the people who can do this job best. We are going to pull them together on a team.

Once we pull them together on a team, we are going to take and assign at least two in depth experts to each section of the ziggurat. Those two in depth experts will go and do two independent reviews of each of the dataset that belongs to that particular section.

They will then come back with their individual, independent reviews to the rest of the team. The rest of the team will act as a peer review committee for those particular interactions. And not until the entire team agrees that we can move forward with that particular step do we move forward with that particular step.

Now, sometimes that means that we need to go back to the sponsor and ask for more data. And trust me, we have. Sometimes that means the answer was pretty straightforward and

we can move forward relatively quickly. Sometimes that means we have to completely redesign a study. And we have. Right?

So I think what is really important to understand about this is this is not a single reviewer's opinion on everything. You have a group of our most senior and experienced reviewers sitting here from every section of the Center. Some of them are sitting back there, too -- don't hide, Hiley*. And it is not until we have unanimous consensus that we move forward. Okay.

(Slide)

So what do we mean by weight of evidence?

What we mean by weight of evidence is unlike for conventional new drugs where we have a pivotal study, we look at all of the information that has been presented.

There are no pivotal studies. Everything is an important study. But some things are more appropriately considered more seriously and are given greater deference than other studies. In the next slide, I will show you how we do that.

But we give sort of qualitative priority to certain sources of data information. We borrow very heavily from the concepts put forward by Sir Austin Bradford Hill in 1954 in his seminal paper on causation where we borrowed the terms "coherent consistency" and "biological plausibility."

When we look at bunches of data, when we do

effectively the meta analysis that constitutes our review, do we see the same kinds of responses in similar studies? Do we see the same extent of responses when we look across studies? And underlying it all, does it make sense with the science?

And if the answer to any of those questions is no, what that means is we have to go back and look harder. And so we did.

(Slide)

So here is our table for how we conducted weight of evidence evaluations. It is in your briefing pack; I am sure you have memorized it. It is actually in a slightly different form in the briefing pack. I prefer it this way where the biological plausibility is the fundament that underlies the entire assessment, okay?

In terms of order of deference, what we have is the first order of deference is a controlled, well designed study of ultimate relevance to the risk assessment question. It has got some good size to it. It is in the spirit of good laboratory practices. It has got a full dataset and it has a concurred protocol.

How often does this happen? Not always.

But the advantage is we have all the rest of these studies that are available in the dataset to support any of those studies. And independent verification from independent sources is the basis of our peer review literature approach.

The reason why you write a detailed material method section in your scientific paper is not to show people that you know what 10 millimolar sodium chloride is. It is because your experiments can be repeated by other laboratories. And the real power of a weight of evidence determination, the real power behind it, is that you can see if results are replicable, okay?

So that is how we did our weight of evidence determination.

(Slide)

So, here is our friend, the ziggurat, back again. And what I am going to do right now it to tell you a little bit about the product definition, how that constitutes things, and then pass things on to Dr. Jones.

(Slide)

The product definition is the fundament on which we build this entire process. It describes the animal, the construct, the proposed claim, and when necessary for purposes of safety or effectiveness, the conditions of use.

The next thing that we look at when we look at this entire ziggurat process is the molecular characterization of the construct where we look at the sequences that are still in the test tube before they go into the animal and ask questions about them. Then we look at what happens to the construct when it goes into the animal and how stable it is over

multiple generations of the animal.

We characterize the phenotype of the animal. We look to see what happens to that animal from both a very gross approach -- behavior, morphology -- all the way down to the fine points of biochemical analysis and the kinds of veterinary records that you would get if you went to a veterinarian as your primary care physician, but not dissimilar from the ones that you would get from your own human physician.

Jay Cormier and Barry Hooberman will tell you about the genotypic and phenotypic durability plan and how they are related to post-approval monitoring and they have to do, again, with insuring the stability of the genotype and phenotype over the lifetime of the product to insure that the animals that we are reviewing now are going to be equivalent to the animals that will be in commerce for the lifetime of the product.

Food, feed, environmental assessment, that is reasonably straightforward; it is what we did to assess the safety of AquAdvantage salmon against its appropriate comparator, okay? Laura mentioned that to you earlier. It is against other Atlantic salmon.

Claim validation -- does indeed this fish do what the sponsor claims it does? And I have already talked to you about that.

So I am going to stop right now and ask if you have any questions for the Veterinary Medicine Advisory Committee. Do you have any questions about our overall methodology?

(No response)

DR. RUDENKO: Okay. If not, let me tell you a little bit about product definition, then; I will start this off.

The product definition is a broad statement that identifies the GE animal, its proposed product or traits, and if required, the conditions of use. We have a suggested format that people may follow or if they come up with a better approach, they suggest it.

So, we like to ask what the ploidy of the animal is. That is not often a problem if you are dealing with a cow, but if you are dealing with a fish, you might have a ploidy issue.

We ask about zygosity -- is it heterozygous or homozygous? We ask for the animal common name or breed or line, its genus and species that contains what copy number, how many copies, of the construct in what particular location and what that animal is going to be called afterwards that does whatever the sponsor says it is going to do under what conditions of use.

So the product definition essentially, when it is done, tells you -- bounds the entire risk and safety assessment that you are going to be looking at.

So now I am going to take you on to the rest and to Dr. Jeff Jones.

Guidance 187 Recommendations for Data Presentation

Molecular Characterization

by Jeff Jones, D.V.M., Ph.D.

DR. JONES: So, I am Jeff Jones. My basic science training is in DNA damage repair, molecular virology and molecular biology. I am also a practicing veterinarian.

My job today is to describe for you the kind of analysis that we conduct for the molecular characterizations.

Molecular characterization is carried out in two phases. First is molecular characterization of the construct. That is where we look at the recombinant DNA construct in the test tube. The second phase is the molecular characterization of the GE animal lineage where we evaluate the rDNA construct as it is stabilized in the lineage of animals that are under development.

(Slide)

The main goals of the molecular characterization steps are to narrow the scope of review from the universe of possible hazards to identify potential hazards, if any, that are associated with a specific rDNA construct and a specific lineage of GE animals under evaluation.

We also confirm consistency with the product definition as we move forward through the hierarchical review

process.

(Slide)

For molecular characterization of the construct, the question that we are asking, or the overall question that we are asking, is: Are there sequences that are likely to contain potential hazards to the animal, humans or animals consuming food from that animal, or for the environment? Practically, the questions that we ask, going through the review process, are:

What is the rDNA construct?

How was that rDNA construct made?

Is the rDNA construct as it was intended?

And, is there any additional useful information available to us as we proceed?

And I will walk you through each of these questions.

(Slide)

The first question: What is the rDNA construct? The little figure on the left is a commercially available construct, a plasmid, and it is there to remind me to emphasize that there are really two parts of the construct. There is the plasmid backbone that is useful for manipulating the construct as you are assembling it and for amplification in bacteria. There is also, on the top, the bar that goes across, there are the inserts that are intended to function in the eventual GE animal.

The diagram on the right is a more stylized version that just emphasizes that there can be multiple components in any of the constructs and that our hazard identification requires that we understand all of the components.

So let us turn to the components themselves.

(Slide)

We want to know if there are any potential hazards associated with the specific components, and we are particularly interested in substances of toxicological concerns and allergens.

The little picture on the left is a lionfish; he is there for two reasons. One is to remind me that fish can be allergens for some groups of people, as can eggs or peanuts for various groups of people. But the lionfish also has a toxin gene, a poison gene, and they have poison in them, so he also reminds me that we have to be thinking about other biologically active molecules in our evaluation.

We also look at the various components in the construct to see if there is junk DNA that is not really well understood because before we move forward, we have to understand that DNA. We also need to know if there are novel sequences or proteins in the construct that need to be evaluated.

(Slide)

Another type of components that we pay close

attention to is mobilizable elements. The figure on the left represents a transposable element, or a transposon, that could allow the construct to move around within the genome of a cell. The virion on the right reminds us that lots of constructs are assembled using either virus vectors or viral components and they can allow the construct to move lots of places. So we need to know about that type of component.

(Slide)

Once we understand what the components in the construct are, we then want to know how the construct was assembled, the process that was used. The figure on the right represents a molecular cloning strategy or scheme.

And our evaluation is to understand the process by which the construct was assembled, the methods that were used. Is the assembly method plausible? Does it make sense? Do we understand any potential hazards associated with that process?

(Slide)

And then we also have to evaluate the data of the final construct. No matter how it was supposed to be put together, we need to know how it really was put together, what the final construct looks like.

And I am showing different kinds of data here -- restriction mapping, PCR with or without restriction mapping, chromatogram showing sequence determination, the contig map for sequence analysis.

Looking at the primary data allows us to understand the data that is being presented to us, the information that we have. The other point of having all these different types of data up here are to remind me that we don't have a specific set of studies that have to be done; we don't have a checklist. We evaluate all the information that is available to us, and if we don't have enough information, we ask for more until we do understand what has been presented.

(Slide)

The second phase of molecular characterizations is the molecular characterization of the GE animal lineage.

Here, we are asking if -- the overarching question: Does the insertion of the rDNA construct into the animal pose a hazard to the animal, to humans or animals -- or humans or other animals by food or feed and/or to the environment?

(Slide)

This figure is to show that the intent of the insertion that we described is really to have a recombination event occur between our region of the construct, the genes of interest, and the DNA of the chromosome of the animal, and of course the DNA makes up the chromosomes and the chromosomes are in the nucleus of every cell in the body of an animal with a heritable DNA construct.

(Slide)

Here, the type of evaluation that we are conducting

is to understand what parts of the rDNA construct went in. Was it just the rDNA construct? Was it the backbone? Was it both? We will talk about that in a second. The copy number of rDNA construct within the cells, the location or locations in the cell, and the final stabilized structure within the GE animal lineage.

(Slide)

Here is our little cartoon again showing the different -- the whole construct. We need to know what went in. Was it just the rDNA construct, the genes of interest with the plasmid backbone, was it everything, what kind of a -- you know, -- was it various combinations of both?

(Slide)

This slide has a number of different figures on it. I want to focus on the top first. Again, we are trying to -- the goal of making an rDNA animal is to put an rDNA construct, represented by the red arrow, into the chromosome, represented by the black line.

The intended rDNA construct can go in, or alternatively, represented by this little black -- little red line here, we could have rearrangements or partial insertion.

We could have, as represented over here on the left, multiple insertions in various orientations at any given location in the chromosome. Or as I am representing over here on the right by different colored lines, we could have

insertions into multiple chromosomal locations.

Finally, we want to know not just about the rDNA construct as it goes into the chromosome, but we also want to know about the interaction between the rDNA construct and the chromosome as well because on a recombination event, we are going to have recombination junctions at both ends of the construct. We want to understand: Does the insertion event interfere with a gene in the chromosome? Is it possible that we have generated a novel protein, a fusion protein, during the recombination event? So that whole characterization needs to be conducted, and evaluated.

(Slide)

Again, we evaluate whatever data is available. And again, it could be the restriction mapping, could be southern analysis, northern analysis, sequence analysis, fluorescence, in situ hybridization. Again, the point is: We don't have a checklist. We evaluate the information that best answers the question: What is the structure of the construct in the genome?

(Slide)

So, through the molecular characterization steps, the -- hopefully, the scope of the review has been narrowed. We have identified any potential hazards that are related to the specific rDNA construct in the insertion site as stabilized in the lineage of GE animals under development, and

hopefully we have provided consistency with the -- for maintenance of the product definition as we are moving forward. I think we are done.

Overview of the Approach to Phenotypic Characterization

by Donald A. Prater, D.V.M.

DR. PRATER: Hi. Good afternoon. My name is Don Prater. I am a veterinarian and an aquatic animal health specialist at FDA and I have been involved with the phenotypic characterization and also the environmental assessment portions of our review. In addition, I have participated in some of the site visits and inspections of the AquAdvantage facility.

And today what I would like to do is give you an overview of our phenotypic characterization section and tell you a little bit more information about what our approach has been. I would like to explain to you what the purpose and value of the phenotypic characterization is as well as the consideration of the types of data and information that we have examined, and we hope that this will be helpful for you tomorrow.

(Slide)

So, a classic definition of the phenotype is the expression of the genotype under a given set of environmental conditions. In our case, we are also interested in the effects of the insertion event and the expression of the

construct.

Characterizing the phenotype helps us understand how the construct affects the animal and it also helps us assess animal safety, but that is not all.

(Slide)

In addition, the phenotypic characterization allows identification of hazards for other steps of the hierarchical review. So when we are looking to identify hazards, we ask ourselves questions such as:

Are there characteristics of the phenotype that would suggest increased or decreased fitness? This helps us understand particular hazards, or identify hazards, for the environmental safety section of the review.

Are there characteristics of the phenotype that might suggest the edible tissue has been altered? This important for food safety.

Or, are there characteristics of the phenotype that would suggest a problem ensuring maintenance of the genotype and phenotype, as is described in our durability plan?

We might also ask if there are any characteristics expressed in the phenotype that would lead us to believe that the intended effect could be lost? That would be important for claim validation.

Or, if the product definition might need to be adjusted? So, for example, if during the phenotypic

characterization we saw sexual dimorphism in the expression of the traits, that might be something where the product definition would have to be readjusted.

(Slide)

So when we consider the phenotypic characterization, we need to look at the potential effects of the construct, and Dr. Rudenko mentioned some of those to you -- indirect and direct effects, the intended effects of the construct versus the unintended effects.

With respect to direct toxicity, we want to consider potential adverse outcomes from the insertion event itself. Is there something that might have caused insertional mutagenesis? We need to look for evidence of cancer.

Also, is there a potential for adverse outcomes associated with the expression of the gene product?

Similarly, indirect toxicities. Are there potential adverse outcomes that we need to consider as a result of the insertion of the DNA construct or from products downstream of the expression product?

We also consider the intended effect of the construct, the beneficial changes. We have to look at those and look at the data parameters that might be important for those as well as any unintended effects of the construct.

The phenotypic characterization is really our best screen for unintended effects of the construct.

And so when we are considering these effects, it helps us to understand what hazards we identify both for the target animal as well as for other steps of the hierarchical review and what is the appropriate type of data and information that we need to consider?

(Slide)

In addition, we also consider the natural biology of the animal and look at any effects of the biologic containment strategies.

So, what are some of the types of data that we look at?

We look at animal health records. These could include physical examinations of the animals, records of veterinary care, general husbandry conditions. It is very important for us to understand the environmental conditions under which the animals are studied and intend to be used.

We can look at production records, growth rates, feed consumption, and reproductive history of the animals.

We also look at behavioral observations, things that I know you are familiar with -- attitude, appetite, their ability to locomote.

Clinical findings -- we look at CBC, chemistry, UA, any post-mortem findings from the necropsy or histopathology.

(Slide)

In addition, we can evaluate other types of data and

information in a phenotypic characterization that might be relative based on the hazards that we potentially identified, so we could look at blood or tissue levels of the gene expression product or downstream elements.

We might look at in-life special tests, or post-mortem special tests.

Basically anything that is a hazard that we identified ahead of time or that comes up during the evaluation, we can look for different types of data and information to try to characterize that hazard and further identify any hazards for other steps of the hierarchical review.

(Slide)

One of the things that is different in considering a genetically engineered animal is that we don’t use one of the classic paradigms of toxicity testing, and that paradigm is the dose response test, the 1, 3, 5X safety study. That is something that you won’t see among our datasets.

I think this would be technologically difficult to accomplish. I am not sure how you would do something like that -- perhaps develop additional GE animals with different copy numbers or things like that. But I am not sure that the information would be likely to be relevant in that case.

So we look broadly at a variety of parameters across many, many animals and multiple generations and we also look

very specifically, with detailed analysis, in a subset of those animals.

And so what are we likely to do with the information from our phenotypic characterization?

We make conclusions regarding animal safety and we identify areas of uncertainty.

This is very important in a risk-based approach to identify both what you know and what you don't know. Identifying areas of uncertainty helps us make decisions about the need for, or an approach to, gathering additional information to make regulatory decisions.

In addition, the phenotypic characterization helps us make recommendations for risk mitigation, labeling -- this is labeling of the type for the GE animals while they are still alive, in transport, -- not the type of labeling as Laura Epstein mentioned for labeling of the product, the food product, derived from the GE animal.

And finally, the phenotypic characterization, as I mentioned, helps us identify hazards for other levels of the hierarchical review such as environmental safety, food safety, durability, claim validation or post-market surveillance. Thank you very much.

Durability

by Joseph W. (Jay) Cormier, J.D., Ph.D.

DR. CORMIER: Thanks, Don. My name is Jay Cormier.

I am a chemist and molecular biologist by training. And today I am going to talk to you about: What do we mean by "durability" in a context of genetically engineered animals?

(Slide)

As Larisa alluded to earlier, durability asks, effectively: is the genotype or phenotype of the product changing over its lifespan in a way that would affect the risk associated with that product? Is there a plan in place to monitor those changes?

(Slide)

So, why do we prepare a durability assessment and why we look at a durability plan?

The purpose of the durability step is to ensure that future animals that go into commerce are equivalent to those that are evaluated for safety and effectiveness during our pre-approval process.

For those of you who had the pleasure of taking Latin and classical studies, this is the Roman god Janus, or "yahnus," the god of New Year, and he is generally depicted with two faces. And the reason for that is one face looks back at the previous year and thinks about what had happened, and the other looks forward to the new year. And just like -- just in a similar fashion, the durability step has both a backward-looking component as well as a forward-looking component.

The backward-looking component asks whether there is data to establish if the sponsor has a product where the genotype and phenotype is stable over time. Has the sponsor demonstrated that in the past they have a product that is consistent?

The forward-looking aspect of the durability evaluation asks whether the sponsor has in place a plan to ensure that those future products will continue to be stable and have the phenotypic and genotypic characteristics that were critical to our evaluation pre-approvally.

And finally, the durability section evaluates the sponsor's commitment to continue to abide by a durability plan and submit that data to the Agency going forward.

(Slide)

So, the genotypic and phenotypic durability evaluation asks whether there are data to suggest that the animal's genotype and phenotype is stable. What do we mean by stable?

Well, I can take a picture of the U.S. Capitol when it was being constructed in the late 1800s and then you can hold it up to the U.S. Capitol today and you can see that they are roughly equivalent. Those two -- that building -- and you might come to the conclusion that that building is in fact stable. The same kind of process applies here. We asked ourself, based on information and testing methods: Is the

animal today roughly equivalent to that which was evaluated before?

(Slide)

The durability plan, again, is a plan to ensure that future animals are equivalent to today's animals. This provides the consumer with expectation consistency with the product and allows the sponsor to continue to rely on the safety and effectiveness data that was evaluated during the pre-approval review process.

In the alternative, if in the event that animals no longer meet the product definition or they are no longer equivalent, what procedures has the sponsor put in place to provide a remedy to either ask the Agency for approval for a change of that product or to go back and regenerate the line of animals at a point in time when those animals were in fact equivalent to that which was evaluated pre-approvally?

(Slide)

And then finally, the sponsor's commitment. It is simply that.

Once the durability plan has been agreed to between the sponsor and the Agency, the sponsor formally commits to carrying out that plan. That provides the Agency with the basis to enforce that plan as it goes forward and the sponsor is legally required to provide that data to the Agency as agreed to in that plan. And that is it.

Food Safety Assessment: Overview and Direct Effects

by Kevin Greenlees, Ph.D., DABT

DR. GREENLEES: Oh, good afternoon. My name is Kevin Greenlees. I am a physiologist and toxicologist, and together with Kathleen Jones, I am the taller one, if you get confused. We will be talking about the -- how we evaluate the safety of genetically engineered animals for food.

(Slide)

You have seen today this picture repeated a number of times, and it is a very important part of our process to talk about the hierarchical peer review. It is probably no more important to anywhere else than it is to the food review process because we rely very heavily on all of those previous steps as we are looking at this review.

If you have a small chemical entity, a new animal drug, a traditional gorillamycin, for example, you know what that hazard is: It is that chemical you have that you are going to administer to the animal.

When you have a genetically engineered animal that you put a construct in, the question becomes: What is the hazard, or are the hazards, that you need to look at? And we rely very heavily on all of those previous steps to tell us what was in that construct in the tube before they gave it to the animal. What was actually administered to the animal?

When you look at the animal, what is actually there

as opposed to what you thought was going to be there? What -- how did that actually express itself in the animal?

We rely very heavily on the phenotypic characterization as a screening tool, as was talked about before, because we believe that the animal itself is a very sensitive tool to look at to say, “Has something changed?” And by looking at that animal very carefully, you might find something that you might need to look at more in depth later, looking for a hazard.

(Slide)

You have certainly heard repeatedly; it is worth mentioning again that our standard is a very high standard for food safety. The standard is reasonable certainty of no harm.

(Slide)

Our approach is to try and identify and characterize the hazards, that we break the hazards for an approach into direct and indirect effects. I will talk a little bit about what we do for direct effects. Kathleen Jones will talk a little bit about indirect effects. In addition, she will talk about the analytical methods which are part of the food safety evaluation.

(Slide)

One question that is often asked is: Why don’t you just test that whole food? And there are a number of reasons why that is not really a practical approach.

For one thing, traditional toxicology testing assumes that you have a nice, pure substance that you can then test in animals, you can test *in-vitro* systems, you can characterize it very carefully, and then you can then quantify the dose response and you can look at it in depth.

Food is not like that. It is a complex mixture. It has a wide variation in composition.

In addition, if you are going to then take that whole food and try to administer it to a test animal, or even look at it in an *in-vitro* system, you very quickly overwhelm the diet of the animal or that *in-vitro* system because you cannot give it in sufficient quantity before you start ruining the animal's diet. You have changed its response simply because you now are giving it this diet versus a different diet, and you cannot give it in a high enough dose to start getting very good sensitivity in your test system.

As a result of that, in general terms, the FDA does not recommend testing of whole foods.

(Slide)

Well, if we are not going to do testing of whole foods, what then do we do? I said we looked at that entire hierarchical approach, and we are looking at the food consumption risks resulting from the expression of the inserted construct as a direct effect. If we find something as a hazard, a result of that, that we can look at, then we

can do toxicological testing on a case by case basis of that direct hazard. That would include allergenic -- allergic assessment testing of proteins new to the food.

(Slide)

We can look at food consumption risks that result from perturbation of the physiology of the animal, for example, nutritional deficiencies that might be identified for compositional analysis. Larisa mentioned other things that might come up that would be potential effects.

Again, we are taking a broad-based, additive effect looking at the entire weight of evidence of that we have for food safety.

(Slide)

Okay -- I thought this went to my colleague, but since it goes to me, you saw this briefly before -- I am not going to go into the same detail that Larisa did.

But what this picture is again intended to show you is that when we look at an overview of food safety, it is fine to look at all of those different components.

So you are looking at the construct. Was there something in the construct that you thought might pose a hazard that you will then have to bring forward to look at in your food safety assessment?

If there was a mobilizable element in there that you thought would be carried through in that construct, did it

actually make it into the lineage of the animal? So that you would then say, yes, it is in the animal; I have to consider it.

If it didn't get into the lineage of the animal or was never into the construct, then that is not something you have to consider as a hazard.

You would look at direct effects: What is actually being expressed by that construct in the animal?

If that construct is producing something like a gorillamycin that you can then say, aha, here is my chemical entity; you can then go off and do traditional toxicological testing on that. You can refine it, you can purify it.

If it is not something like that, if it is another food component that is being expressed, well, then, you have to decide: Is it something you can look at in traditional toxicology or do you have to look at it under this other approach we are looking at, the general composition of the animal.

You can look at indirect effects, which is something that, again, my colleague will talk about in more detail.

Or there are things that are a result of the insertion of that construct into the animal that might cause a change in food that has to be evaluated.

(Slide)

And now we are in fact into Kathleen's section.

Food Safety Assessment: Analytical Methods and Indirect Effects

by Kathleen Jones, Ph.D.

DR. JONES: Thank you, Kevin. My name is Kathleen Jones, and my particular area of expertise is in the safety assessment of foods from genetically engineered organisms. And I am going to talk to you a little bit about analytical methods.

There are two different kinds of analytical methods for GE animals. The first is for a tolerance and the second is for identity.

(Slide)

With respect to an analytical method for tolerance, this would only be needed in cases where hazard has been identified and would be present in the food. Also, of course, it would only be needed in food-producing animals.

(Slide)

The second type of analytical method is for identity. And because the safety and effectiveness are established for a particular construct and a specific insertion event, it is important to know that this GE animal that is in commerce can be proved to be derived from a GE animal lineage that was approved. Therefore, for all GE animal NADAs, an analytical method for identity will be needed.

(Slide)

This provides a list of characteristics for an analytical method for identity. Basically, it needs to be able to be able to identify the approved GE animal or edible tissues from a GE animal from either non-GE or other GE animals. Specifically, it should be able to discriminate between an approved GE animal product and a “me, too” GE animal.

The method also needs to be sufficiently robust to be practical, to be used in a field laboratory.

In addition, it could also provide useful information if there is a durability failure. For example, the analytical method for identity could not only -- could also be part of the durability plan.

And I think that is it for food safety -- at the 100,000 foot level.

Environmental Safety Assessment

by Eric Silberhorn, Ph.D., DABT

DR. SILBERHORN: Good afternoon again. I am Eric Silberhorn. I am a member of the Environmental Safety Team in the Office of New Animal Drug Evaluation. I am an environmental scientist with training in fish biology, toxicology and ecological risk assessment. We will talk about the environmental safety, the more the scientific basis today rather than the regulatory basis that I talked about this morning earlier.

(Slide)

Again, the environmental safety assessment comes near the top of the hierarchical review process after we have collected a lot of data on phenotype and genotype and molecular characterization. And the general overarching questions we are trying to answer are, again similar to -- for the safety assessment, the other safety assessments are: What are the direct or indirect effects from introduction of the animal into the environment?

(Slide)

To remind you again, I don't usually give this talk after giving a full-blown NEPA talk, but just to remind you that the regulatory requirements here are a little bit different and that ultimately we are trying to make this determination of whether the approval action may significantly affect the human environment, and it is triggered by an Agency action under an NADA, and ultimately the outcome is going to be a finding of No Significant Impact or a decision to prepare an Environmental Impact Statement.

(Slide)

So, there are some general risk questions that will help lead us to determine whether there could be direct or indirect effects. And they must be considered considering the potential conditions of use and context of the product definition that we are talking about. So everything is done

on a case by case basis.

But -- and for the environmental assessment, I guess there is something unique in that. We are mainly going to be concerned about escape from -- of animals from facilities, but there is potential to have actual free release and there are animals being currently developed as biocontrol agents that might be intentionally put into the environment, and actually there already are examples of this in this in the insect literature -- you know, fruit flies and things like that that are intentionally sterilized and put into the environment.

So there is a -- conceptually, that will have a large impact on the kind of questions you would ask and the direction the risk assessment might take. So this being a general high level talk, I am just going to talk about both free use -- or free release and escape. So we are --- the potential of the risks under conditions of use which would normally be conditions of confinement.

We are interested in: What is the likelihood of escape and free release? And that is going to take into consideration the number of containment measures and the adequacy and the redundancy in those containment measures. And I will go on to detail on some of this in the following slide.

We are looking at the likelihood of establishment and reproduction, and then potentially, if those things were

to occur, what would be the potential adverse outcomes associated with that?

(Slide)

Again, it is important that you have an appropriate comparator. So the comparator for an escape scenario could be substantially different than the comparator for a release scenario, intentional release scenario.

So if this concern is over escape, then we may be looking at the farm equivalent -- so, in other words, a goat being housed, or let us say a pig, because it is more likely to become feral, a pig housed in a farm that were to escape. The comparator would be other pigs, other natural pigs, farm pig.

If we were looking at intentional release, we are going to be maybe concerned about with the wild relatives of that animal and conspecifics, related species that it could interbreed with.

(Slide)

So this is -- I am going to go through this slide and I will be coming back to it tomorrow, so hopefully it will -- would like you to understand it.

Starting up here, this is our model for hazard risk assessment, taking -- starting with a source or a facility, in most cases it is going to be a facility, but where GE animals would be housed. And then our ultimate concern is here over

direct and indirect effects and then potential impacts from those effects. But you can see there are different ways to get to this box here where you might have direct and indirect effects. You have to take into account escape or in cases of intentional release.

The accessible environment around those facilities, the ability of the animal to survive in those accessible environments, the ability to reproduce in that environment, and then from there, the animal could possible disperse into other adjacent environments, could establish, and then from there, you have the potential for direct and indirect effects. And also, if you are able to reproduce, then you could end up spreading the transgene either to related wild versions of the conspecifics, in other words, the same species in its wild state or related relatives.

(Slide)

So, there are other things that will come into play here, and that is containment. So everything has to be done in consideration of containment, which is usually considered to be a type of risk mitigation.

Physical containment can prevent this release into the environment, and as we said earlier, if there is no exposure, then there can be no risk. So, essentially if we stop the exposure right here to the environment, there can be no direct or indirect effect.

Some of the other things that come into play that can affect ability to get down here is geographical and geophysical containment, things like environmental factors -- temperature, salinity, things like that -- that affect the animal's ability to survive in the environment and its ability to disperse to other environments.

And again, by those forms, different forms, of biological containment which would essentially stop this here and prevent an animal that might be able to survive but it would prevent it from being able to actually reproduce in the environment; therefore, it is not possible for that animal to establish, at least on a long-term basis, which would again preclude indirect and direct effects through that pathway.

(Slide)

So, I mean, the bottom line here is that you need to look at all these different types of factors, but the important thing is it has to be done in the context of these different types of containment.

(Slide)

So, this -- again as an overall talk or a high level talk, when doing assessments, environmental assessments, on GE animals, there are some general considerations that come into play. And prioritizing those include the ability of the animal to disperse into different communities if it were to escape or be released; its fitness within those environments,

and the components of the environment itself and how resilient and stable that environment is.

And the product -- the overall consideration is based on the product of this concern, not just the individual sum of these factors.

(Slide)

All right, to get into a little more specifics, so when we are trying to determine what are the possible consequences of an introduction or escape and dispersion of a GE animal, it is going to be based on a lot of different factors. So this again has to be done on a case by case basis, based off this hierarchical review process where we look at phenotype and genotype and other factors.

But it depends on the physical locations where the use is going to be or the animal might be held; the extent of containment, as I said earlier, physical, biological and geographical; and niche limitations that might be inherent in those environments around those locations.

Other things that come into play are the domestication of the species and its ability to become feral, so certain species are much more likely to become feral -- mice, pigs. Certain fish can become feral much more likely, so that comes into play whether that animal is likely to establish in the environment.

And also another factor which will affect dispersion

and potentially the amount of escape that could occur is the mobility of the species.

(Slide)

Ultimately, fitness comes into play if there were to be escape or intentional release and there will be some, I think, additional talk about this tomorrow by Dr. Hallerman, but net fitness is something that we get information from the phenotypic characterization, gives us information on net fitness. And net fitness includes both survival and reproduction and it is typically, in laboratory studies, the factors that are evaluated include things juvenile and adult viability, age at sexual maturation and fecundity and mating success.

(Slide)

Ultimately, we are trying to determine how the rDNA construct might affect an animal's fitness. And some examples of change fitness that is potential, that could potentially occur, are disease resistance and enhanced or reduced disease resistance; a change in physiological tolerance -- in other words, ability to survive different temperature and salinity condition. Could be changes in growth hormones or growth factors which could affect all types of physiological end points. And ability to utilize nutrients in carbohydrates. And some of these are, you know, are being done intentionally to give different animals agronomic traits.

(Slide)

So, ultimately -- I am not going to go into a lot of detail, but the direct and indirect effects really have to be looked at on a case by case basis. Some of them, again, some of the things that we might be interested in are the pathogen disease transfer, genetic disturbance, resource competition, displacement, habitat destruction, ultimately -- and predation. Ultimately, we are concerned about population changes and from there, how those population changes might influence communities or ecosystems. That is the higher level type of assessment that might be done if there were effects at this level. And that wraps it up. Thank you.

Claim Validation

by Evgenij Evdokimov, Ph.D.

DR. EVDOKIMOV: Good afternoon. My name is Evgenij Evdokimov. I have expertise in molecular biology and analytical chemistry. And the focus of my presentation today is the claim validation step of the review process.

(Slide)

So the previous steps of the hierarchical review process approach primarily address identity and the safety issues. And this step will be pre-market review process. We evaluate whether the GE animal meets the claim established in the product definition. So in other words, we have to make sure, we have to find an answer to the question: Does the

animal what the sponsor claims it does?

(Slide)

So, for example, if a cow -- if we have a cow that is resistant to a certain disease, we have to make sure that that cow is indeed resistant to that disease.

Or, for example, if a sponsor designed a chicken capable of producing therapeutic proteins in the egg white, we need to make sure that those proteins are indeed present in the egg whites.

(Slide)

So where do we get the data for the evaluation of this step?

The data and the extent of the data required for the claim validation are unique for each application.

The sponsor may design a study and execute that study that specifically addresses the claim. We also draw on the data and the conclusions from the previous steps of the hierarchical review process.

First, we look at the product definition. The product definition forms the basis of the review process, it forms the foundation. The information that we have in the product definition drives the subsequent data generation and the review process.

Next, we look at other steps of the hierarchical review process to see whether they contain any information

pertaining to the claim.

(Slide)

So what kind of data do we look at when we evaluate the claim?

If we -- if the product definition is talking about the expression of the molecular -- especially on the protein, we may look at the molecular characterization of the expression product. So this includes, but not limited to, ELISA, protein electrophoresis gels, mass spectrometry data.

If the product definition is talking about the presence of the certain trait, like for example, animal disease resistance, heat conversion efficiency, or the altered nutrient composition, we need to take a look at the data that confirm the presence of those traits in the animal. And now we go probably to the questions. Thank you.

Deliberative Process

by Aleta Sindelar

(Slide)

MS. SINDELAR: Hi. I am Aleta Sindelar. I will be talking on the -- I apologize for my lack of technical skills here. I am going to speaking on the deliberative process. And essentially, when will the VMAC members deliberate?

The VMAC members will deliberate following all of the presentations made by the speakers for the meeting, following all of the public comments made during the open

public comment hearing. That includes the registered speakers and speakers that will be able to speak from the floor that will not be registered.

After all of the questions by the Committee members to the speakers and after all the clarifications regarding the charge to the Committee, at that time the Committee will deliberate.

What is the deliberative process? It is a general discussion amongst the members. It is also a specific discussion on the charge from the FDA. They are comments on questions to the Committee. And then there will be a summary of comments by the Chair.

Two weeks following this meeting, you will be able to find this on our Advisory Committee website in the form of our transcripts.

(Slide)

Our general discussion begins with the Chair assuming charge of deliberations. He may ask the VMAC if they have any additional questions of any speaker, guest, FDA or public during those deliberations. He leads the discussion of presentations among the Committee members.

During deliberations, a Committee member may have additional questions, but Dr. Senior may direct towards the appropriate speaker.

At the conclusion of the general discussion, Dr.

Senior may invite comments from the Committee regarding the first question of the charge. The specific discussion on the charge to the Committee is such that FDA is seeking comment from the VMAC on each question of the charge.

When the Chair believes that all comments have been received for each question, he will move on to the next. At the conclusion of comments on all questions, Dr. Senior will make a summary statement.

Following this, the Chair will relinquish the mic to the Center Director for closing remarks and adjournment.

(Slide)

Questions for today's orientation session. We will first select from the VMAC members the questions of the FDA speakers.

After these have been answered, questions of clarification may be asked by the public. Please submit your questions for clarification on distributed note cards, and we have Eric, Malini, Brinda and Annie to distribute note cards and pens.

No questions about the Particular Matter of the meeting will be allowed from either the VMAC members or public.

(Slide)

Thank you for time and attention today.

DR. DUNHAM: Thank you, Aleta, very much, and I

thank all of our speakers this afternoon. That was a very, very good overview. I really do hope that you have all enjoyed this educational afternoon.

Questions and Answers from VMAC to Agency Experts

And now we will be able to have the VMAC Committee ask some questions. But, first and foremost, our Chair, has a comment. Thank you.

DR. SENIOR: This comment is to the Committee. As you know, we will be asked to discuss four issues.

In the interest of complete and thorough discussion of the issues, I will be asking each member in turn, each member of the Committee in turn, for their assessment of the strength and weaknesses of the evidence data we have been presented and that we will hear relative to the questions that were encouraged.

If you miss a point or another point occurs to you after you hear discussion from another individual on the Committee, don’t despair; there will be the opportunity to get back to you. I will make sure that everyone’s voice is heard on the issue and that we have completed our discussion before moving on to the next point.

I would ask you -- we have a very full -- we have a very, very full agenda tomorrow with fairly larger and complex issues to discuss -- if you have a point to make but a previous Committee member seems to cover that point very

excellently before you -- I know there are quite a few university professors on this Committee, including myself -- I would ask that you refrain from spending too much time on your reassurance that the previous Committee member was on the right track in your opinion. Of course, if you disagree, that is -- absolutely speak up.

So with that, I will ask the Committee members if they wish to ask any questions of the speakers. Robert?

DR. POPPENGA: I guess I have one question that -- with regard to the first charge to the Committee to decide whether that -- I will make a comment about the rDNA construct being safe to the salmon.

I am little bit confused between maybe safety and animal welfare issues. I have heard both comments today. Can you talk -- address the issue of safety to the salmon versus maybe other animal welfare issues?

DR. RUDENKO: Hi. Well, we are not going to do with the Particular Matter at hand. The issue of animal health and animal welfare is one that comes up on a frequent basis and we can talk about it from a generic perspective right now, if that will be helpful.

DR. POPPENGA: Yes, it is just clarifying animal safety versus animal welfare, in a generic sense.

DR. RUDENKO: I think animal health -- a lot of it depends on how you define animal welfare. There is a set of

statutory authorities that are administered by the U.S. Food and Drug Administration called the Animal Welfare Act --

MS. : No, no --

DR. RUDENKO: I am sorry, I am sorry -- it has been a long day. Have a drink! That are administered by USDA that are referred to as the Animal Welfare Act. And they deal particularly with issues that are associated with animal welfare such as transport, bedding -- bedding for purposes of comfort, things like that. I am not an expert, and I am mistaken, I am sure that other people in the audience will correct me very quickly.

On the other hand, the issues that are associated with animal health also take into account some animal welfare issues. Is the animal in general good health? Is the husbandry, standard husbandry that is provided for these animals, sufficient to insure their good health? So, does the -- do animals behave appropriately, given their particular health issues?

I hope that gives you some context. They are -- it is not a bright line between the two, and we take a -- we tend to take a rather broad view towards animal health. Don, do you want to add anything to that?

DR. PRATER: I think that is a very good question, and typically we look at animal health parameters under the new animal drug regulations and we don't really get into

issues of animal welfare. And so importantly here, I think we are looking at the condition of the GE animals relative to other commercial salmon -- or, I am sorry -- other commercial animals. Thank you.

DR. SENIOR: I have a question. The -- it is about the jurisdictional separation and partition, I guess, jurisdictional partition, with respect to this Committee's deliberations.

The VMAC normally would, I think, look at the approval of -- or the request for a New Animal Drug Application relative to a product that would be introduced to the animal and then would -- there would be a period in which the product might disappear from the animal and then the consideration such as food safety would be relative to withdrawal times et cetera.

And I am thinking in this context the product is introduced in the animal and then stays with the animal and I am just wondering to what extent this comes under the food side of the Food and Drug Administration rather than the drug side of the Food and Drug Administration and why that aspect would be necessarily the purview of the Center for Veterinary Medicine and why it would be the cause for the VMAC to deliberate this issue.

DR. DUNHAM: I will start, and our legal will probably follow through. But basically what we are looking at

is any drug that changes structure function of an animal comes under the purview of review at the Center for Veterinary Medicine. They also are key to review any product that will come from the animal receiving said drug from which there will be an item for human consumption.

We then jointly, as you will see, many times work with the Center for Food Safety and Applied Nutrition. They will often look at other aspects. But we do the first aspect if that is within the animal from which you will then have a product that will be for consumption by humans or goes into feed for other animal consumption.

So the first paradigm does come back to: What are we looking at? A drug approved for humans? A drug approved for animals? And so we do that first review. Laura?

MS. EPSTEIN: As Dr. Dunham was referencing, I think the answer to your question is that CVM combines both elements. It is both drugs and food within one Center.

And historically what happened was before there was a Section 512 of the Federal Food, Drug and Cosmetic Act that created these New Animal Drug Applications, for a new animal drug you had to have two applications. You had an application that was a drug application that was looked at the same way that a human drug is and that is why that standard derives from there and it is this risk benefit balancing. And then you had to have a separate application for a food additive,

and that is the food piece. So now it is combined into one application.

But you are right -- there are two pieces here. There is a food piece and there is a drug piece. And that harm standard that we were referencing before is the food -- same as the food additive standard. It is now in the New Animal Drug Application piece. So that is why there -- CVM actually combines those pieces together for new animal drugs.

DR. SENIOR: So the important aspect with respect to this is that this is still an Atlantic salmon. This is still the same animal. We are not allowed to discuss that.

MR. : Tomorrow!

(Laughter)

DR. SENIOR: Tomorrow.

DR. DUNHAM: Today, we are just doing a very broad education of the process --

DR. SENIOR: Yes.

DR. DUNHAM: -- and we are trying to keep it at that level. Tomorrow, we will be very focused.

DR. SENIOR: Any other questions from the Committee? Mike?

DR. APLEY: Dr. Rudenko, one of your slides have been -- sitting here thinking about how to ask this correctly, but in safety you referred to it as a balance of risk and benefit for animal health.

I have -- this is just a point of clarification for me -- I have watched multiple processes go through the FDA CVM and have had it explained it to me. As I understood it on multiple times, it is about risk analysis rather than a risk benefit analysis. So I was kind of surprised to see this. Like when we look at other issues of antibiotic resistance or those uses and we say, are we going to balance the risk with the benefit? And the response I have gotten is no, no, no, it is evaluating the risk, it is their job.

So is that -- have I misunderstood that when we look at other issues or --

DR. RUDENKO: I am going to take a quick run at this and then let my colleagues, particularly Ms. Epstein and possibly Dr. Greenlees, address it.

I think the issue here is that it is a standard for animal health. And when one looks at antibiotic resistance, one is looking at a larger public health perspective.

Here what we are doing is -- as it is with every drug -- we take a look to see what the benefit to the animal is versus the risk to the animal. There is not a specific standard that says “no more than 0.02 percent of the animals shouldn’t have an adverse outcome.” It is an intrinsic balancing. Just as, for example, for the food standard, which is relatively straightforward -- it is reasonable certainty of no harm -- the Agency accepts the fact that there is no such

thing as zero risk. And the best way that we can express that, the most stringent way, we have to express that as "reasonable certainty of no harm."

MS. EPSTEIN: I don't know if I really have anything to add to it.

I think mostly what you are looking at is a risk analysis, and that is why that is what you focus on. And it depends on the new animal drug what you are doing with the benefit piece of it.

There are many new animal drugs where the intent is sort of to increase, say, production of the animal, things like that, and that might not be as straightforward of a balancing test as it would be with, say, you know, let us say -- I don't know whether the same for a human where you have a chemotherapy drug, for example, and it is highly toxic but you are looking at, you know, a benefit for a patient that has no other options and that kind of a straightforward risk benefit balancing. And, I mean, that is true of other products that FDA regulates as well where the risk benefit is going to vary depending upon the facts, where you are looking at something that has a cosmetic benefit, for example, versus the example that I was just giving.

So here, there is still -- that is still the test, but you are mostly focusing on: What is the risk analysis? Are there are any risks there? How severe are they? And that

is why most of the discussion is going to focus on that.

DR. WELLS: I don't recall who all used this term, but I saw several times the term "human environment." And I am having a hard time understanding exactly what the definition of that would be. So could someone describe what the non-human environment is that counteracts that?

(Laughter)

DR. SILBERHORN: Well, fortunately, I might actually be able to find the actual NEPA definition. It -- I just may happen to have it here and can read it to you. It is -- human is overarching but, you know, it means that the interaction of humans with their environment, so it is supposed to mean we are not strictly looking at an ecological effect, in other words, just on animals in the environment, excluding how that might affect humans. So that is why they use that term rather than strictly "environment," effects on the environment. It is the effects on human environment, trying to take into account that interaction.

But if you hold on a second, I can probably read the whole definition to you. You can never find these things when you need them.

Okay, so this is out of the NEPA regulations, 1508.l4: "Human environment shall be interpreted comprehensively to include the natural and physical environment and the relationship of people with that

environment. See definition of effects." And I talked about effects.

This means that economic or social effects are not intended by themselves to require preparation of an Environmental Impact Statement. "When an Environmental Impact Statement is prepared and economic or social and natural or physical environmental effects are interrelated, then the Environmental Impact Statement shall discuss all of these effects on the human environment."

DR. MATHEW: I just wanted to know what was the timeline for the expert review of the data for this particular case? And does the FDA feel confident that the timeline was not overly aggressive so that literature review and full, comprehensive review of the data was possible?

DR. RUDENKO: We can talk about that tomorrow --

DR. MATHEW: Okay.

DR. RUDENKO: -- in detail.

DR. KANEENE: On Page 49 of the slide presentation, I have been trying to put my arms around this --- how you assess durability, how -- I mean, that -- I am having a problem comprehending how you do that. Do you have time in mind in terms of this? I don't want to mention the species but can you expand on that? I am just having a problem putting my arms around that.

DR. CORMIER: If I understand your question

correctly, you are asking: How is it that from a molecular point of view we think about durability?

DR. KANEENE: Yes, from this GE.

DR. CORMIER: In the backward looking part of that?

DR. KANEENE: Yes.

DR. CORMIER: So what we look at when we are assessing durability is we determine, based on the information that we have from the molecular characterization of the GE animal lineage -- we have information as part of what the construct is, where it is specifically located, and what confirmation is it sitting in the genome -- and we can use data and information to verify that that construct is still present at the same location and is not replicated in other places within the genome, hasn't changed copy numbers, hasn't -- and that from one generation to the next, that construct continues to be durable from -- and stable from one generation to the next. And I think what you are alluding to is intergenerational time periods might be dramatically different depending on the species.

DR. KANEENE: Right.

DR. CORMIER: So we are not -- we don't have a per se rule that says "X-number of generations are required to demonstrate durability." It is -- again, as with all of the steps, it is a weight of evidence approach. So you will hear some more things -- well, let me rephrase.

If the construct ends up in a place in the genome where we would expect a lot of change within that genome based on our understanding of genomes, then that might be something that we would want to look more in depth at. If it is in area that might be considered to be sort of a, quote, safe harbor to the extent that one exists in a genome, that might -- all of that information is taken together to help determine whether we feel confident that the inserted construct is stable at its location.

DR. KANEENE: Thank you.

DR. EENENNAAM: Yes, I have a question for Eric regarding the effects in the NEPA. And specifically could you explain the term “social effects?” What would be covered under that? As I understand it, that is something that should be considered in NEPA.

DR. SILBERHORN: Well, it may be considered. It has -- it is only considered if it is relevant. And so here is where I am trying to emphasize that everything, because it is a case by case basis on our point in the context of conditions of use.

The social, economic, aesthetic, cultural, those things may or may not be relevant. If they are relevant, they need to be considered, but only if they are relevant.

So -- and they are not defined. Those aren’t defined in NEPA as they are very general, and the reason for

that is because the NEPA regulations apply to all agencies so it could cover any kind of action including promulgation of regulations ---. So they are very general terms and so there is a lot of flexibility and not a lot of specifics on what those have to cover.

But the important thing is that in FDA I will say this: We rarely look at those effects and have rarely looked at them in our environmental assessments. We have normally focused on ecological and environmentals, you know, traditional ecosystem type of end points. Does that answer your question?

DR. THORGAARD: I have got a question for Laura Epstein. I was just kind of interested in understanding more about the importance of precedents in, you know, FDA decisions, and this particular case seems to be a fairly kind of a new -- going into new territory. But in general, is there a large role for kind of precedent in FDA decision processes?

MS. EPSTEIN: I actually don’t know if I am the best person to answer that. But I do think that, you know, as the Agency interprets safety over time, looking at different particular products, that experience I think informs future evaluations.

But it is very fact specific, so I think it is, you know, only where you are going to have various products where

you look back and there is something that you evaluated before that is relevant. Obviously, if it is apples and oranges, the precedent really isn't going to have any effect. And here we are looking at something so new, as you said, that I don't know. It is sort of early to be talking about precedent, you know.

DR. THORGAARD: Well, I had a kind of a specific case, but maybe it is more appropriate to bring up, you know, tomorrow.

DR. POPPENGA: I am trying to get my head around this environmental assessment and if I just read this here maybe generically, are any potential environmental impacts from X-production adequately mitigated under the proposed conditions of use?

I guess I am wondering about production, and does that include an assessment of either biological or pharmaceutical wastes or is that regulated by other agencies?

DR. SILBERHORN: Well, I can say in general -- and our regulations changed on this in 1996 -- but at one time FDA included as part of their environmental assessments analysis of manufacturing in the -- of potential effects on the environment from manufacturing, which included facilities in foreign countries. So you would typically -- your environmental assessment would cover those things and if you had manufacturing in Italy or China, whatever, those had to

cover those things. That was changed in our -- when our regulations were updated in 1996 and so now we typically do not include a strict evaluation of manufacturing because we believe that those are effectively regulated by other agencies or other countries, so usually the EPA, and EPA has specific effluent guidelines that have been promulgated for pharmaceutical manufacturing and also for aquaculture also.

And so that is the general assumption. There are exceptions when we still look at environmental impacts from manufacturing facilities, but that is, again, the exception, not the rule. Did that answer your question?

DR. POPPENGA: Yes. I am just trying to figure out then if those aspects are covered by another agency, then to what extent does that agency have input on your environmental assessment and the decision then to go into an environmental impact study?

DR. SILBERHORN: Well, under NEPA we are required to consult with other agencies when we believe they have information of particular relevance or have the expertise that we don’t have. So that is something we do.

And we typically work a lot with EPA on, say, aquaculture drugs, which I am heavily involved in, so we consult with them on issues and coordinate to make sure that drugs are being effectively regulated by one agency or the other. So I would say that is something that is part of our

process, our normal process.

DR. McKEAN: Yes. The question relates to durability. As I have heard -- what I thought I heard in the explanation was that durability is limited to construct -- durability, is that correct?

DR. CORMIER: If I left that impression, that was an incorrect one. The -- with respect to the durability assessment during the pre-approval evaluation, we determine both genotypic and phenotype durabilities. That assesses both the stability of the construct as well as the stability of the effect of that construct within the animal with respect to animal safety and effectiveness.

DR. McKEAN: Okay. And that goes to the genesis of my question.

DR. CORMIER: Okay.

DR. McKEAN: As you go forward, how does the durability plan take into account things like changes in environment, changes in places where these -- this construct may show up, and genetic drift?

DR. CORMIER: So specifically with respect to the genetic drift in the genotypic changes, we expect our sponsors to have in place a series of tests and methods to insure that the genotype of the animal, it remains consistent through the future.

With respect to the interaction of the genotype with

the environment, the approval is limited to specific conditions of use of various -- of whatever genetic engineered animal is present, and so that is considered to be part of it. And if those conditions of use are thought to change in a post-approval setting, that kind of change would be part of what we would consider to be a post-approval supplemental application, so that would be considered at that time.

So -- but the sponsor is limited to the conditions of use as agreed to during -- for the approval itself going forward. Any changes to that, again, is something that comes in under the rubric of post-approval changes.

DR. McKEAN: Yes, I am less -- so far, you have described -- pretty much limited your description to the genome and you said that if both phenotypic and genotypic evaluations. And I am thinking there may be more phenotypic opportunities for drift.

DR. CORMIER: My apology. With respect to phenotypic durability in the post-market setting, the Agency will continue to rely on the adverse event -- where it is considered like adverse event reporting drug experience reports.

So if an individual who is aware of certain events that would suggest a change in the phenotype of the animal afterwards, they can report that voluntarily to the Agency. If the sponsor is aware of such information, they are required

to provide that information to the Agency. So, through a combination of the durability plan, the conditions of use, as well as the normal ADE DER -- I am sorry -- Adverse Drug Event reporting and Drug Experience Report, we anticipate being able to collect the kind of information that will allow the Agency to evaluate the genotypic and phenotypic durability of the product in the future. Does that --

DR. McKEAN: I think that goes far enough.

DR. CORMIER: Thank you.

DR. SENIOR: I believe there are no more questions from the Committee.

Audience Questions Read from Note Cards

DR. DUNHAM: Thank you very much. We will now proceed. We have had a few cards come forward and we will give you some responses to some of the questions.

I get to do the easy one:

"In assessing the GE salmon safety for human consumption, how many people have had the opportunity to taste this GE salmon?"

DR. DUNHAM: And I think you all know the answer to that. We will discuss that one tomorrow. Isn't that great? I get to do everything! Okay, Larisa, you have the next one.

DR. RUDENKO: There is a question that asks:

"Could we confirm that the product claim validation process does not constitute a benefits analysis on the

product?"

The answer is yes.

And then:

"Will the VMAC be asked to vote on answers to the question?"

Most emphatically: Not.

The VMAC will be asked to provide recommendations and to discuss thoroughly. We are not asking you to vote on whether or not to approve this. We very respectfully and sincerely ask for your discussion and your open comments, as we do from the public as well.

Next question was:

"How were the FDA reviewers selected?"

And the answer was I went to Bernadette and said, "I need the best we have got. Can you please free them up from other things?" And:

"How long did their review of AquaBounty EA take?"

We will talk about that tomorrow.

And here is another question that is sort of outside the remit of this meeting but we will take a little run at it:

"Why do you feel there was so little public resistance to the 2008 GMO goat approval?"

I have -- I think the important thing there was it was a joint meeting with CBER, the Center for Biologics Evaluation Research, and we presented our materials as part of

their overarching review. And I have no idea why there was less -- why there was not a big response to that. Is there one from Eric?

DR. SILBERHORN: Yes, I have a question:

"If you used farmed equivalents as the only comparator for the genetically engineered animal, please clarify what genetic and ecological traits do you require data for the farmed equivalent and the genetically engineered animal."

And, I mean, all I can say is that, again, we do these things on a case by case basis. We obviously have a very small N at this point, so we are still learning to a certain extent.

But it really depends on if it is a terrestrial animal, it is an aquatic animal, how it is housed, the conditions of use. So it is a case by case. It is a risk-based. We look -- you know, we have these risk questions; we will get more into that tomorrow. But we will use that -- the conceptual risk model that I showed you, and we look at that in the context of physical, biological and geographic containment and try to ask more specific questions.

We don't have a set of checklists, we don't have, you know, a general cookbook, that we go by, so that is about all I can say there.

MS. EPSTEIN: There is a question about whether a

sponsor's proprietary studies of food safety and environmental safety study are ever released in full or if FDA only provides summaries of the sponsor's data.

No, it is not typically the practice of the Agency to release all the data. I mean, sometimes data can take up a whole room, so it is sort of hard to release that much data. But with this, this has really been an unprecedented release of information at the time of the meeting.

DR. RUDENKO: I think I would like to just add a tiny bit to that. There is often a Freedom of Information summary that is released post-approvally. What is unprecedented about this release is that it is pre-approval.

We have an environmental assessment question that actually I am going to answer. It is my turn. So I am not sure I fully -- the question, slightly rephrased, is whether or not the environmental assessment only considers the particular hazard that is formed posed to the environment or are there other hazards considered in the environmental section such as the construct, portions of the construct, the integration form, or what are the other hazards?

And I think the answer is: Absolutely. The whole point of this hierarchical weight of evidence, risk-based review is that you cannot complete any of the upper levels without considering all of the lower levels of the analysis. So you cannot do a risk assessment until you have identified

all the hazards. The reasons why the hazards are identified at the beginning is so that you can carry them through the entire analysis.

Okay, and I think that wraps up our questions.

DR. DUNHAM: Well, we actually did manage to complete the entire afternoon and we are going to get you out of here before 5:00.

I want to thank everybody for your attendance. Your participation means a lot to us and we really want to thank the presenters who did a fabulous job today. I really hope that has helped to clarify things for you and we look forward to having you come back tomorrow at 8:00 in the morning and we will start the VMAC, so thank you all and have a very pleasant afternoon.

(Whereupon the meeting adjourned at 4:45 p.m.)