



U.S. Food and Drug Administration

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Veterinary Medicine Advisory  
Committee Meeting

**AquAdvantage Salmon**

September 19 - 20, 2010

*Sunday,  
September 19, 2010*

**Sponsored by the**  
US Food and Drug Administration,  
Center for Veterinarian Medicine  
Rockville, Maryland

**Held at the**  
DoubleTree Hotel  
Rockville, Maryland

*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.

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

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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

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

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

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

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

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

25           Dr. Craig Altier is Associate Professor, Department

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

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

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

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

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

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

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

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



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

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

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

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

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

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

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

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

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

6 ***The Role of the VMAC Committee Member***

7 ***by Aleta Sindelar***

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

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

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

1 Committee meeting.

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

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

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

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

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

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

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

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

16           (Slide)

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

22           (Slide)

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

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

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

11 (Slide)

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

20 (Slide)

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

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

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

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

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

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

17 (Slide)

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

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

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

6           (Slide)

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

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

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

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

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

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

13           (Slide)

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

17           (Slide)

18           When does FDA convene an Advisory Committee meeting?

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

24           (Slide)

25           What is the value of VMAC?



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

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

10           (Slide)

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

13           (Slide)

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

21           (Slide)

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

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

4           (Slide)

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

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

15           (Slide)

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

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

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

4 (Slide)

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

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

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

20 (Slide)

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

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

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

14                           ***Genetic Engineering: An Overview***

15                           ***by Larisa Rudenko, Ph.D., DABT***

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

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

23                           (Slide)

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

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

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

8 (Slide)

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

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

18 (Slide)

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

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

3 (Slide)

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

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

16 (Slide)

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

1 (Slide)

2 So, how did we start domesticating animals?

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

16 (Slide)

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

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

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

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

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

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

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

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

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

19 (Slide)

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

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



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

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

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

12 (Slide)

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

15 MR. : Gem.

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

20 MR. : Gem.

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

24 (Slide)

25 So, assisted reproductive technologies, as I

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

4           These techniques differ from genetic engineering,  
5 and here I would like to introduce you to Petunia, who is our  
6 genetically engineered pig. Petunia has a gene that has been  
7 introduced into her and she has a trait that she is  
8 expressing. The trait is the star. We don't really know what  
9 the trait is because Petunia is a generic pig for us, but  
10 Petunia can either have that trait introduced as a non-  
11 heritable construct or as a heritable construct, and Guidance  
12 187, which we have written and which has undergone the  
13 notice/comment process and that Ms. Epstein will be telling  
14 you about, addresses particularly animals with heritable  
15 constructs.

16           (Slide)

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

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

25           Genetic engineering, on the other hand, introduces a

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

7 (Slide)

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

11 In point of fact, we have got all these technologies  
12 -- genetic engineering is not the be-all and end-all; genetic  
13 engineering is not a panacea for anything; it is simply a tool  
14 in the 21<sup>st</sup> century toolbox. Included in that tool are -- is  
15 everything from breeding to marker-assisted breeding to doing  
16 genome-wide studies to genomics, perdiomics, metabolomics.  
17 All this other stuff that has been developed in the last 15 or  
18 20 years aids us in trying to identify the kinds of traits  
19 that we think would serve animals and humans best.

20 Now, how do those traits aid us?

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

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

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

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

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

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

2                 And then we can also develop high value products.

3     There are people at the University of Wyoming who are

4     developing goats that have spider silk in their milk. Why

5     would you want to have spider silk in the milk of a goat?

6     Well, that material can be spun so thinly and so finely that

7     it can be used as ballistic protection devices.

8                 So these -- this is the range of kinds of materials

9     and products that can come out of genetically engineered

10    animals.

11                And on the left hand side of the page are all the

12    tools that can go into -- you noticed I said "genetically

13    modified animals." All of these traits, all of these

14    techniques, can be used to modify them. Only some of those

15    techniques are genetic engineering.

16                (Slide)

17                And what we are going to talk to you about today is

18    how that started. All of you know that the principles of

19    heredity were first described by Gregor Mendel in 1865, who

20    demonstrated that there were indeed some traits that could be

21    predictively passed from parent to offspring.

22                (Slide)

23                Martha Chase and Alfred Hershey -- I don't think he

24    is the "chocolate Hersey" at all -- first demonstrated to us

25    that DNA was indeed the material that transferred the genetic

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

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

12           The structure of the genetic code was determined not  
13 just by Watson and Crick but by Rosalind Franklin as well in  
14 1953. We have to stick up for our sisters here.

15           (Slide)

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

21           (Slide)

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

25           Paul Berg and Herb Boyer did the basic recombinant

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

6 By 1982, we were beginning to develop genetically  
7 engineered food crops, and the first food crop that came to  
8 the Agency was the Calgene Flav'r Sav'r Tomato, okay?

9 (Slide)

10 So how do we make a genetically engineered animal?

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

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

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

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

10           So, moving forward.

11           (Slide)

12           So how do we actually get to making an animal?

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

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

22           (Slide)

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

25           (Slide)



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

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

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

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

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

1 (Laughter)

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

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

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

12 Thank you very much for your time.

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

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

17 MR. : (Away from microphone)

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

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

1                   *New Animal Drug Approval Process Applied to GE Animals*

2                   *by Laura Epstein*

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

10                  (Slide)

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

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

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

23                  (Slide)

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

1                   And the answer is: Yes.

2                   (Laughter)

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

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

11                   (Slide)

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

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

18                   MS.                   : 2009.

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

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

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

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

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

20           (Slide)

21           Well, why is this construct a drug?

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

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

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

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

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

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

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

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

11           (Slide)

12           So how does FDA regulate genetically engineered  
13 animals?

14           (Slide)

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

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

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

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

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

13            (Slide)

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



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

4 (Slide)

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

16 (Slide)

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

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

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

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

14 (Slide)

15 So what are the standards for approval?

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

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

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

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

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

9           (Slide)

10          And how is that now going to apply here?

11          (Slide)

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

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

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

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

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

11           (Slide)

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

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

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

1 of the human environment?

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

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

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

14           (Slide)

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

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

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

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

1 safety standard.

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

6           Do the data indicate that AquaAdvantage salmon grow  
7 faster than their conventional counterparts? There is the  
8 effectiveness.

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

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

20           (Slide)

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

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

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

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

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

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

4 (Slide)

5 So what will the process be?

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

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

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

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

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



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

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

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

17                           *National Environmental Policy Act (NEPA)*

18                           *by Eric Silberhorn, Ph.D., DABT*

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

25                           (Slide)

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

9           (Slide)

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

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

18           (Slide)

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

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

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

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

17           (Slide)

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

1 (Slide)

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

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

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

21 (Slide)

22 So what does FDA do under NEPA?

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

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

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

15 (Slide)

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

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

25 So the next step would be to move to environmental

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

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

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

14           (Slide)

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

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

1 (Slide)

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

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

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

17 (Slide)

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

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

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

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

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

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

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

22 (Slide)

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



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

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

16           (Slide)

17           So, what is an environmental assessment?

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

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

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

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

21           (Slide)

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

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

25           But in reality what happens most of the time is that

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

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

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

19           (Slide)

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

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

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

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

11           (Slide)

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

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

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

3 (Slide)

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

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

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

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

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

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

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

12 (Whereupon, the Committee took a break from 2:27 to  
13 2:50 p.m.)

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

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

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

1 session. Thank you. Dr. Rudenko?

2 ***Introduction to the Regulation of GE Animals at FDA***

3 ***by Larisa Rudenko, Ph.D., DABT***

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

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

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

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

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

1 Do I need to say it one more time?

2 (No response)

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

6 (Waving of hands)

7 DR. RUDEENKO: --- how about now?

8 MS. : (Away from microphone)

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

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

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

18 (Slide)

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

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



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

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

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

15           There are a couple of important take home messages  
16   here.

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

1 they are covered by enforcement discretion.

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

10           (Slide)

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

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

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

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

25           At the moment, because a piece of DNA generally

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

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

12           There are specific considerations of the conditions  
13 of use.

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

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

24           (Slide)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

10           (Slide)

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

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

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

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

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

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

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

13           (Slide)

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

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

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

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

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

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

10 (Slide)

11 Okay, so now, hazards and risks again.

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

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

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



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

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

6           (Slide)

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

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

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

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

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

6           (Slide)

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

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

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

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

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

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

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

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

17 (Slide)

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

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

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

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

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

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

16 (Slide)

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

25 The way that we did this assessment was to pattern

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

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

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

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

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

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

10 (Slide)

11 So what do we mean by weight of evidence?

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

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

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

25 When we look at bunches of data, when we do

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

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

8 (Slide)

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

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

21 How often does this happen? Not always.

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

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

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

10           (Slide)

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

15           (Slide)

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

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



1 multiple generations of the animal.

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

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

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

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

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

4           (No response)

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

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

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

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

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

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

3                   ***Guidance 187 Recommendations for Data Presentation***

4                   ***Molecular Characterization***

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

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

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

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

18                  (Slide)

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

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

1 process.

2 (Slide)

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

10 What is the rDNA construct?

11 How was that rDNA construct made?

12 Is the rDNA construct as it was intended?

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

15 And I will walk you through each of these questions.

16 (Slide)

17 The first question: What is the rDNA construct?

18 The little figure on the left is a commercially available  
19 construct, a plasmid, and it is there to remind me to  
20 emphasize that there are really two parts of the construct.  
21 There is the plasmid backbone that is useful for manipulating  
22 the construct as you are assembling it and for amplification  
23 in bacteria. There is also, on the top, the bar that goes  
24 across, there are the inserts that are intended to function in  
25 the eventual GE animal.

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

5           So let us turn to the components themselves.

6           (Slide)

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

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

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

24           (Slide)

25           Another type of components that we pay close

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

8 (Slide)

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

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

17 (Slide)

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

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

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

9           (Slide)

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

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

16           (Slide)

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

24           (Slide)

25           Here, the type of evaluation that we are conducting

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

7 (Slide)

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

13 (Slide)

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

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

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



1     insertions into multiple chromosomal locations.

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

12                (Slide)

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

20                (Slide)

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

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

4 *Overview of the Approach to Phenotypic Characterization*

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

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

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

21 (Slide)

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

1     construct.

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

5             (Slide)

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

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

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

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

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

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

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

4 (Slide)

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

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

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

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

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

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

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

6           (Slide)

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

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

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

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

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

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

24           (Slide)

25           In addition, we can evaluate other types of data and

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

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

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

13 (Slide)

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

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

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

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

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

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

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

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

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

23 *Durability*

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

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

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

4 (Slide)

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

10 (Slide)

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

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

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



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

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

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

14           (Slide)

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

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

1 animal today roughly equivalent to that which was evaluated  
2 before?

3 (Slide)

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

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

17 (Slide)

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

20 Once the durability plan has been agreed to between  
21 the sponsor and the Agency, the sponsor formally commits to  
22 carrying out that plan. That provides the Agency with the  
23 basis to enforce that plan as it goes forward and the sponsor  
24 is legally required to provide that data to the Agency as  
25 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

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

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

10 (Slide)

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

14 (Slide)

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

22 (Slide)

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

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

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

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

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

19           (Slide)

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

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

4 (Slide)

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

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

13 (Slide)

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

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

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

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

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

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

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

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

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

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

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

24 (Slide)

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

1                   ***Food Safety Assessment: Analytical Methods and Indirect Effects***

2                   ***by Kathleen Jones, Ph.D.***

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

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

11                  (Slide)

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

16                  (Slide)

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

25                  (Slide)



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

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

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

14           And I think that is it for food safety -- at the  
15 100,000 foot level.

16                           *Environmental Safety Assessment*

17                           *by Eric Silberhorn, Ph.D., DABT*

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

1 (Slide)

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

10 (Slide)

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

20 (Slide)

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

1 on a case by case basis.

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

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

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

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

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

3 (Slide)

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

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

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

18 (Slide)

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

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

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

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

16           (Slide)

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

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

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

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

14           (Slide)

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

19           (Slide)

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

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

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

6 (Slide)

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

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

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

25 And also another factor which will affect dispersion

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

3 (Slide)

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

14 (Slide)

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



1 (Slide)

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

13 ***Claim Validation***

14 ***by Evgenij Evdokimov, Ph.D.***

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

19 (Slide)

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

1 animal what the sponsor claims it does?

2 (Slide)

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

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

10 (Slide)

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

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

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

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

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

1     pertaining to the claim.

2                     (Slide)

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

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

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

16    *Deliberative Process*

17    *by Aleta Sindelar*

18                     (Slide)

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

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

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

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

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

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

16 (Slide)

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

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

25 At the conclusion of the general discussion, Dr.

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

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

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

11 (Slide)

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

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

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

23 (Slide)

24 Thank you for time and attention today.

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

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

4                               *Questions and Answers from VMAC to Agency Experts*

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

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

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

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

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

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

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

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

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

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

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

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

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

3 MS. : No, no --

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

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

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

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



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

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

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

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

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

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

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

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

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

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

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

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

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

12 MR. : Tomorrow!

13 (Laughter)

14 DR. SENIOR: Tomorrow.

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

17 DR. SENIOR: Yes.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

7 (Laughter)

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

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

22 Okay, so this is out of the NEPA regulations,  
23 1508.14: "Human environment shall be interpreted  
24 comprehensively to include the natural and physical  
25 environment and the relationship of people with that

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

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

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

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

16           DR. MATHEW: Okay.

17           DR. RUDENKO: -- in detail.

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

25           DR. CORMIER: If I understand your question

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

3 DR. KANEENE: Yes, from this GE.

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

5 DR. KANEENE: Yes.

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

20 DR. KANEENE: Right.

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



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

10           DR. KANEENE: Thank you.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 process, our normal process.

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

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

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

15 DR. CORMIER: Okay.

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

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

25 With respect to the interaction of the genotype with

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

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

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

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

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

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

8 DR. McKEAN: I think that goes far enough.

9 DR. CORMIER: Thank you.

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

12 *Audience Questions Read from Note Cards*

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

16 I get to do the easy one:

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

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

23 DR. RUDEENKO: There is a question that asks:

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

1 product?"

2 The answer is yes.

3 And then:

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

6 Most emphatically: Not.

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

12 Next question was:

13 "How were the FDA reviewers selected?"

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

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

18 We will talk about that tomorrow.

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

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

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



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

4 DR. SILBERHORN: Yes, I have a question:

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

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

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

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

25 MS. EPSTEIN: There is a question about whether a

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

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

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

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

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

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

4 Okay, and I think that wraps up our questions.

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

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

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

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