

Food and Drug Administration

Center for Veterinary Medicine

Veterinary Medicine Advisory Committee Meeting

November 4, 2003

PARTICIPANTS

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John T. Waddell, D.V.M., Chairperson
Arthur L. Craigmill, Ph.D.
Sherman (Skip) W. Jack, D.V.M., Ph.D.
Deborah T. Kochevar, D.V.M., Ph.D.
John J. McGlone, Ph.D.
Lisa Nolan, D.V.M., Ph.D.
Marguerite Pappaioanou, D.V.M., Ph.D.
Anne M. Parkhurst, Ph.D.
Dennis P. Wages, D.V.M.
Richard R. Wood

FDA, CVM STAFF PRESENT:

Amy Adams, Ph.D.
Eric Dubbin, D.V.M.
John Matheson, Moderator
Larisa Rudenko, Ph.D.
Aleta Sindelar, R.N.
Stephen Sundlof, D.V.M., Ph.D., Director

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November 4, 2003

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M O R N I N G S E S S I O N

9:02 A.M.

MS. SINDELAR: Could we have your attention to begin the meeting, please. Thank you. My name is Aleta Sindelar. I am the Executive Secretary for the Veterinary Medicine Advisory Committee. I would like to introduce Dr. Stephen Sundlof, our Center Director, Center for Veterinary Medicines. And welcome you all here this morning. Thank you.

Welcome and Introductions

by Dr. Stephen Sundlof, Director CVM

DR. SUNDLOF: Thank you and welcome everybody. We haven't had an advisory committee meeting in a while and so it's really good to see a lot of folks that we may not have seen for a while.

We are here, again, to talk about the cloning risk assessment that CVM has been conducting as part of our orderly and transparent process of dealing with one of these very complicated issues that is resulting from modern technology.

Before we begin the discussions today, let me introduce the members of the Committee. The Chairman is Dr. John Waddell. If you could just signal with your hand.

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Thank you, John. Corrie Brown could not be with us today. She represents pathology.

Art Craigmill, one of our new members from the University of California Davis, representing toxicology. Skip Jack. Skip represents minor species on the Committee. Dr. Deborah Kochevar, representing small animal medicine. John McGlone, another one of our new members representing animal science.

We have Lisa Nolan, representing microbiology. Mark Papich, who represents pharmacology, could not be with us today. Marguerite Pappaioanou, from the Centers for Disease Control and Prevention, representing epidemiology. Anne Parkhurst, who we hear is in the house. There she is. Hello, Anne. And Anne is representing statistics, biostatistics.

And Dennis Wages, who is representing poultry medicine. And it looks like something fell off the bottom of the screen. Oh! Richard. Dick.

(Laughter.)

It wasn't intentional Richard. We are particularly happy that Richard Wood is representing consumers. He has represented consumers on this Committee for many years. And we have asked him back by special request to fill that very, very important role, since this particular issue has so many

consumer implications.

So those are the members of the CVM Advisory Committee, just to orient people as to who they are. And I think before we move on, and I wanted to get this in the beginning of the program, we have some awards to present to our outgoing members.

And the first one I want to present, and I don't know if she is in the audience, is Dr. Barbara Glen. Oh, she is here. This is a U.S. Food and Drug Administration Advisory Committee Service Award presented to Barbara Glen in recognition of distinguished service on the Veterinary Advisory Committee. Come on up, Barbara.

DR. GLEN: Thank you very much.

DR. SUNDLOF: Thank you.

(Applause.)

DR. SUNDLOF: Our next plague goes to Dr. Anne Parkhurst. She slipped out. Oh, there she is again. I keep losing you Anne for some reason. Come on up. It says the same thing, for distinguished service in her service on the Veterinary Medicine Advisory Committee. Thank you very much. It's been a pleasure working with you.

(Applause.)

DR. SUNDLOF: And finally, Dr. Deborah Kochevar. We hate to see all these fine folks leave us, but hope you

have had a good experience with the Committee. Thank you very much.

(Applause.)

DR. SUNDLOF: Okay. Just to orient you a little bit and give you some context about some of the issues that CVM is wrestling with right now, as new technologies develop and food safety issues and animal safety issues come to our attention, there are really three areas. We are only going to be talking about one of those today.

(Slide)

And the three areas are things like gene therapy. As you will recognize most of these issues are also issues for human medicine. Transgenic and the one, again, that we will be talking about today, is cloning. Probably the most straight forward of those three.

CVM's primary responsibility in this area is food safety, which is pretty much always our mission. We are also very concerned about the safety to animals.

(Slide)

We have produced a risk assessment on cloning. We have circulated and published a summary of that, in an 11 page summary. The overall risk assessment will come out later. Let me just explain a little bit about the situation that occurred there.

We did receive a very large data set in June of this year. That data set has been fully analyzed. But, because of the amount of information it was just not possible to get the final report in the form that we thought was suitable for publication.

We did not want to postpone this meeting as a result of that because we basically have come to the conclusions that are represented in the summary document. So we will be publishing the full risk assessment. It will be somewhere on the order of 250 to 300 pages, largely tables and appendices and those kinds of things.

That will be circulated for public comment. And no final decisions will be made, of course, until that has undergone a thorough public review.

So, there has been a major effort going on within CVM to develop this risk assessment. It is part of a larger process. I don't want to give people the impression that this is the only thing that we are doing.

So, to provide some context, I will talk about the process by which the risk assessment really fits into the overall policies and regulations that the FDA will ultimately come to in determining what the regulatory status is of cloned animals.

(Slide)

This started -- the whole process really started with the birth of Dolly the sheep. At that point in time we recognized that this technology had the ability to be introduced into larger agriculture. It did have many benefits that could be useful to agriculture.

And so we have been very much engaged with the scientific community and the people who have been the developers of this technology to track the progress of it as it moves closer and closer to actual commercialization.

Once we understood that this was likely, this technology was likely to become a much bigger than laboratory experimental science, we contracted with the National Academy of Sciences. And the Academy, we asked the Academy a number of questions, not only on cloning, but on transgenic biotechnology as it applies to animals in general. And that committee did produce a very valuable report that was published last year.

We took very seriously the conclusions and the recommendations of that report. And one of the conclusions of the report and recommendations was that we conduct a more thorough risk assessment, taking into account all available knowledge that exists. And that is what we have tried to do.

Again, this is one part of the process, identifying the risks to the food supply and the risks to animals is very

important to CVM in our mission to protect public health and animal health.

There will be other parts of this as we go along. And one of those will be a risk management document that we expect to be published sometime late Spring of 2004 that will take into account the finalized risk assessment after the public has had an opportunity to review it and comment. And then look at what possible regulatory options we have in order to make sure that any risks are adequately managed.

So we are going to present today the results of that risk assessment. The idea here and what we have said all along, is that as we reach certain milestones in this process, that we will make all of that information available to the public.

And this is part of that process. So that is what we are doing today. It doesn't infer any final policy decisions on the part of the FDA. It is merely to say this is where we are in our determinations. We want to make sure that everybody has access to the same data. None of the data that we will use in making our decisions are proprietary. They will all be in the public domain. And so we want to make this as much a transparent process as possible.

(Slide)

Here are the questions, some of the questions, that

we will address during the next, or today. And the question is do the risks experienced by animals involved in the cloning process differ qualitatively from those experienced by animals undergoing other assisted reproductive techniques, such as embryo transfer and in vitro fertilization, some of the techniques that are widely used in animal agriculture today.

(Slide)

The second question that we will be asking is, are the edible products derived from animal clones and their progeny as safe to eat as the edible products derived from their conventional counterparts. I think everybody is aware that that is our critical area of concern.

(Slide)

Our initial conclusions would include, we want to get some idea about the frequency of animal health problems. Although some of the problems that have been identified from clones may be similar to those with other assisted reproductive techniques. Is the frequency different? And does that frequency, is the frequency of those abnormalities declining over time as the technology improves?

Food from adult clones, again, are food from adult clones as safe as those from conventional animals? We are using these classifications based on age. So the question

here really talks about adult clones versus cloned animals that may be at earlier life stages. And that discussion will take place today.

(Slide)

So based on what we have presented, what we will have presented here today, have we adequately identified the risks relating to animal health? We need to have your input on that.

(Slide)

And then based on what we have presented, have we adequately addressed the risks to public health? Very simple questions, but have all kinds of complexities built into them. So your review on this, as the Committee, is extremely important to us.

I think it's extremely important to the public to get the expert opinion of an outside scientific body such as yourself. And your expertise, again, will help us make the kind of informed decisions that we need to as a public safety regulation, or regulatory agency.

So, again, thank you and I look forward to a productive meeting. And now let me introduce to you, Dr. John Matheson.

Brief Background For Today's Discussion

by Mr. John Matheson, Moderator

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MR. MATHESON: But before we get on with this show today, Aleta Sindelar, our executive secretary, has a conflict of interest statement to read to the Committee.

MS. SINDELAR: Before we begin our deliberations, this is important for the public record to know that we have thoroughly addressed any conflict of interest issues that may pertain to the Committee. And this is of general matters. So as bureaucratic as this may sound excuse me for reading.

"The following statement is made part of the public record to preclude even the appearance of a conflict of interest at this meeting. The associate commissioner for external relations FDA has appointed Mr. Richard R. Wood, Drs. Deborah T. Kochevar and Anne M. Parkhurst as temporary voting members for this meeting.

Based on the agenda, it has been determined that the Committee will not be providing advice on specific firms or products at this meeting.

The topics being discussed by the Committee in open session are considered general matters issues. To determine if any conflicts of interest exist, the agency reviewed the agenda and all relevant financial interests reported by the meeting participants.

The Food and Drug Administration prepared general matters waivers for special government employees who required a waiver under 18 U.S.C. 208. Because general topics impact on so many entities, it is not prudent to recite all potential conflicts of interest as they may apply to each member.

FDA acknowledges that there may be potential conflicts of interest, but because of the general nature of the discussion before the Committee, these potential conflicts are mitigated.

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

Waivers are available by written request under Freedom of Information Act. Thank you for this opportunity."

MR. MATHESON: Thank you Aleta. Good morning. My role this morning is to talk with you about how we got to the risk assessment process. What steps have been taken. And to provide some basic definitions so that we are all working from the same background as we go through the risk

assessments.

Cloning of animals with known genetic merit.

"Known" is the key word here because of somatic cell nuclear transfer is the first process that allows us to copy animals that we know their genotypes. We know whether they will be male or female. We will know what the adult animal looks like. And that is what makes it commercially possible or feasible.

(Slide)

Not all cloning is about productivity, although you will hear a lot about that. The longhorn in the middle has been cloned because of the horns, of its rack. It's a rack on a cow. And the two calves below it are the clones.

You will also notice there are no poultry in this picture. Somatic cell nuclear transfer has not been accomplished with poultry to any great extent so they are really not a part of this risk assessment.

(Slide)

Our goal in this whole process of risk analysis with animal cloning is to provide a science-based decision making platform of the future decisions for risk management. To provide some education to ourselves and to the public about cloning.

For the process to be transparent so that all data

that we use in making the decision is available to the public and they can understand how we used it. And that we eventually establish a risk management process that is proportionate to the level of risk, other than fit it into a preexisting framework. We wanted to assess risk first.

(Slide)

As Dr. Sundlof mentioned, we have been going through this process now since early 2000, late 1999, when it became evident that a number of firms were becoming interested in commercially copying animals. Again, this is just clones, or just copies.

We met with them starting early in 2000 and encouraged each of them to publish safety data. Now, we were a little naive, I guess. The safety data are hard to get published because there is a bias against boring old safety data. So we did find out, the hard way, that there is this bias in the literature against providing information that animals are not significantly different from other animals. It just doesn't sell journals.

At the same time when we were meeting with these firms, starting in 2000, we were asking them to not introduce these food products derived from these animals or their progeny into the food supply. We made that request public in July of 2001. And at the same time in 2000, we contracted

with the National Academy. So that process took two years for them to make the report that was delivered partly about clones and partly about the rest of the science based issues with animal biotechnology in September 2002.

(Slide)

At the same time we co-sponsored with the PEW initiative on food and biotechnology, a public meeting on animal cloning in Dallas. Many of you were there in the audience. I don't think any of the advisory committee was present.

We think that --. Well, we know that the report was issued in June of '03 so you can see that on the PEW initiative site as well as hear all the presentations. They are all still mounted on the PEW site. It was a live webcast.

In the meantime we were preparing the risk assessment and we are now reaching the final stages. This advisory committee meeting is part of the process to preview the risk assessment, which will later, we hope soon, be available in its entirety for everyone to comment on.

So any comment period doesn't really begin until the full risk assessment is out there. We plan to release it on our website, again because books of this nature, it's about 300 pages long, will not be published anyplace. You

cannot get the full data sent or the full risk assessment published in a journal for example.

(Slide)

Now some definitions. We have mentioned somatic cell nuclear transfer as a term that we are applying to cloning. This is the type of cloning that we are discussing here. It's the, you can read the definition. It's the fusion of the nuclei of a diploid donor with unfertilized enucleated oocytes. Say that three times.

(Laughter.)

Clone. That is an animal resulting directly from somatic cell nuclear transfer. Or animal clone. You will hear that term used. We don't usually try to say cloned animal because you really don't know when you say cloned animal whether you are talking about the donor, the cell donor, which would be the large horse in that picture, or the actual clone. So we try to say animal clone or clone when we are referring to the product of somatic cell nuclear transfer.

And cloned progeny are offspring of at least one parent who was a clone that are sexually reproduced. So not a clone of a clone. But a sexual reproductive product of the clone.

(Slide)

Again, just to remind we are talking just copies, not genetically engineered animals. In our view these things occupy different risks faces. We would do a different kind of risk assessment for the genetically engineered animals.

(Slide)

This slide from Cyagra, thank you Ray Page, summarizes the process for somatic cell nuclear transfer. One point to make here is that in the second slide where it says "insertion of donor cell", if the donor cell is a somatic cell, then you have somatic cell nuclear transfer. If the donor cell is a blastomere cell from an early stage embryo, then you have blastomere nuclear transfer. That is really about the only difference between these two types of cloning.

Again, the blastomere nuclear transfer is an earlier process that is on the market, has been in the marketplace and has been in our food supply for a number of years. It was not particularly commercially successful because you really don't know the genetic potential of that blastomere cell. You don't even know if it's a male or female.

(Slide)

So is somatic cell nuclear transfer really part of the continuum of assisted reproductive technology? Or is it

something different? Is there something unique in the way of the hazards presented by this technology to both animals or food that justifies special regulations? Or is it like all the others that are listed here ending with blastomere nuclear transfer. That is what "BMT" stands for.

Embryo splitting has been out there for some time, as well as in vitro fertilization and artificial insemination. So that is really the crux of the matter here. Is it part of the continuum or is it something unique that we need to assess?

(Slide)

Presentations this morning will focus first on risk assessment methodology. Dr. Rudenko will present that. We will have some data summaries from Dr. Dubbin. I think we will have a break somewhere in there.

We will also have animal health risk conclusions from Dr. Amey Adams, who is in the audience. And then Dr. Rudenko will return for a food consumption risk conclusions. We will call them tentative conclusions at this stage. And that is really what this morning will take. Then we will have lunch.

So with that, I will introduce Dr. Rudenko and we will begin the serious business of assessing the risk of this technology.

Risk Assessment Methodology

by Dr. Larisa Rudenko

DR. RUDEKNO: Well, good morning. My name is Larisa Rudenko. I am the senior advisor of biotechnology at the office of new animal drug and evaluation at the Center for Veterinary Medicine. I would like to thank you all for coming today. It's nice to see so many friendly faces in the audience.

(Slide)

I am going to start my talk first of all by thanking several of the clone manufacturers who have graciously provided us with wonderful photos that we have used here for visual interest. There is an acknowledgment slide at the end. Unfortunately Dr. Bob Wall from USDA fell off that slide. So I will reward him specially by calling him out at the beginning. Those are his little piggies backs that you can see back there.

As both Dr. Sundlof and John Matheson had said, this is part of an orderly and transparent process that we are initiating here at the Center for Veterinary Medicine, or rather continuing at the Center for Veterinary Medicine. Especially on a topic of new technology that has so much attention called to it because of the newness of the technology itself and for other issues that surround it as

well.

What do we mean by transparency and how do we initiate a transparent process with the public and with you, the advisory committee? Well, a scientist or a risk assessor sees transparency as making the rules clearly available and understandable to everyone.

We need to define our terms. We need to show you our work. We need to clearly apply the rules to our work so that you can see where our conclusions are coming from. And then we need to tell you what we don't know and what we do know. What we surmise and what we deduce.

And so what I hope to be able to do in the next 40 minutes or so is walk you through how we made the rules. How we applied the rules. What we applied the rules to. The terms that we used. What we know from the data. And what we don't know from the data.

I will be assisted by Dr. Eric Dubbin and Amey Adams in the actual presentation of the data and the conclusions from it.

(Slide)

Again, as John has told you, we had a charge and that charge was to characterize risks to animal health for animals that are involved in the cloning process and to humans and animals from the consumption of food from animal

clones or their progeny.

As we said before, and we really need to emphasize this, this specifically excludes genetically engineered animals. So there are no trans genes involved here at all. The other point that is very important to make as part of this open and transparent process is this is the first step. This is the introduction and roll out of the risk assessment. It is not a discussion of risk management.

(Slide)

So you all have seen this triad of risk assessment, risk management, and risk communication. As part of our defining of terms, we are going to tell you what we mean by risk assessment, risk management, and risk communication.

(Slide)

Risk assessment, or the step that we are on right now, or more precisely the step we are introducing to you right now, is science based. It identifies hazards and risks. And we will talk about the difference between the two in a couple of minutes. It's relatively value free, but never entirely value free, because we do make assumptions, but we try to be very clear about what those assumptions are. And finally, it provides a framework for risk management decisions.

Risk management, on the other hand, which will come

farther along in the process, is the identification and evaluation of alternative strategies and the selection among them based on some set of preestablished criteria.

And finally, risk communication, which is part of what we are involved in right now, is the interactive exchange of information and opinion among scientists, among regulators and among the public. And we are grateful that you are here to share this with us today.

(Slide)

So again, how do we approach this? Well, we had a statement of our goals. We considered traditional risk assessment methodologies. We tried to determine whether or not those would fit the issues presented by cloning or not. We did a survey of the literature when we started on this process and I became involved in it in about July 2002, I guess it was.

We surveyed the literature to see what there was out there. And then we asked some very fundamental questions about what hazards might be involved in cloning and what risks might result from those hazards in order to help develop a framework for what we were going to do. And then we went back and reviewed the literature within that context.

(Slide)

So, in terms of starting out from a baseline, the

first place to go always when you are looking at risk assessment is to the National Academy of Sciences who have published similar works on the issue.

In the right hand column you will see the four steps of risk assessment that have been made, I guess, famous or infamous, depending on what your position is, from the 1983 National Academy of Sciences Redbook.

Those four steps are hazard identification where you talk about what might happen if exposure occurs. And exposure assessment determining the extent and nature of the exposure.

A dose response evaluation, which is a toxicological review of the kinds of effects you see at varying doses when you are exposed, or laboratory animals are exposed to a particular substance.

And the risk characterization, which is a qualitative and quantitative melding of the information that you gathered from the previous three steps.

Well, in the 2002 report on animal biotechnology that the National Academy of Sciences put out, they came up with a slightly revised set of steps for risk assessment. The first one said, well, you have to identify the harms.

The second one said identify the potential hazards that might come from those harms. Determine what the

exposure means and the likelihood of exposure. That is fairly similar to the exposure assessment step. And then quantify the likelihood of harm given that exposure has occurred.

Note that both of these approaches imply that there is a specific etiologic agent involved. You are exposed to something. The amount of that thing may change. That thing may cause bad things to happen.

(Slide)

Well, bear that in mind and now let's go back to our literature search. When we did our initial survey we came up with about, oh, probably about 1,000 hits on our literature search survey, maybe 2,000.

By the time you went and threw out duplicates and so forth and so on, we identified about 500 papers that might be relevant to animal somatic cell nuclear transfer. Most of these papers describe the technology development. We used this kind of a cell, we got this kind of fusion. We used that kind of a cell, we got that kind of fusion. We applied an electrical pulse that worked. We did a chemical pulse that didn't work. Those kinds of studies.

Many of these studies, including many of the key studies that are cited in reviews of cloning, especially reviews of cloning that address adverse effects that are

noted are actually on transgenic animals. And that is not clear in many of these papers unless you actually traced the papers back to their original citations.

The emphasis on these papers, as John had said, is hypothesis testing. That is what journals publish. They want unique data where you test the hypothesis or report on something new. There are very few surveys of animal health. And those surveys that have been cited most often in the press address transgenic clones. Again, and that is not always obvious.

So by the time we whittled down through there, we ended up using probably about 100 papers in our overview of which probably 60 to 65 percent were completely relevant. We also investigated model systems for the livestock species that we are interested in. And we looked at mouse as a model system where there is a fair amount of publication.

(Slide)

So, harms, hazards and risks. What is the hazard here? The little jug that the goat is climbing on, what is the risk? The little goat might fall.

(Slide)

So, hazard is an act or a phenomenon that has the potential to produce a harm. And a harm is defined as an adverse outcome, an injury, or some kind of loss or

detriment.

And, finally, risk, in this context, is the conditional probability that an adverse outcome will occur provided that exposure has occurred. So that is a quantitative --. That definition can be incorporated into a quantitative or a qualitative expression of risk.

(Slide)

So what were our challenges as we went forward in doing this risk assessment? Well, we needed a methodology that was suitable for both animal health and food consumption risks. That is not necessarily a short order.

We have to get down to what the potential harms might be for both animal health (AH) and food consumption (FC). Our pledge was that everything that we would evaluate would be publicly available. That somewhat limited what we could look at.

We didn't have a theoretical framework for cloning to start with. We had no etiologic agent. We had only a technology change. We had no inserted genes. No resulting gene products. And no postulated pleiotropic effects from insertional mutagenesis as one might hear from transgenic animals.

So there we were. That made the risk questions very difficult to formulate and the absence of risk, or

safety as we sometimes think of it, difficult to prove. If foods appeared to be the same, if animals appeared to be the same, how could we prove that? How could we limit the uncertainty that came with that question or with the answers?

And, finally, what metric would we use? How would we measure risk? What would our comparative group be? That is where we started from.

(Slide)

Well, we also started with a couple of baseline assumptions. We said if animal clones were to be considered for food, they would not be considered any differently, or not subject to any less stringent rules than conventional animals would be subject to.

So we assumed that there would be compliance with existing regulatory requirements for conventional food animals and for food derived from conventional animals.

(Slide)

We also assumed, as has been the assumption of toxicologists and physiologists for a very long time, that domestic animals consumed for food do not naturally produce toxins in their edible tissues. And that frankly diseased or defective animals do not enter the food supply. That is conventional animals or clones should they approach the food supply.

If that is the case, and we have no transgenic inserts and we have no frankly diseased or malformed animals entering, then the changes that could be seen, that could occur in these animals would likely be due to gene dysregulation or what are known as epigenetic changes. And because by definition you can't see these changes, we called them subtle hazards.

(Slide)

Now subtle hazards are something that are outside the conventional range of food hazards as we understand them. I spent 20 years doing food safety risk assessment and we never talked about subtle hazards before.

So what could those food hazards be if we were to postulate them? Well, we could say there might be changes in gene expression as a result of somatic cell nuclear transfer. And those might result in phenotypic variability such as coat color, behavior, and longevity.

And if you look at any twin humans in the population you will see that they have different freckle patterns. They might have slightly different hair coloration. They have different fingerprints. Those are all the result of epigenetic changes.

It's possible to postulate disruption of the immune function. And that might be a risk to the animal or to the

food supply and manifested as increased sensitivity to pathogens. So we need to look for that.

And then the last thing are subtle changes in the metabolism of an animal such that the animal has changes in its physiological set-points. It compensates for those physiological set-points. But you might have levels in tissues of certain substances that might be higher or lower than you would expect. And that might pose some kind of a nutritional risk to you. Because you might not get the vitamins that you are expecting or some key dietary component that you are looking for.

So the next question we asked ourselves, well, this is fine. This is a fine theoretical construct. We like this. But how would these differ from subtle hazards that arise in conventionally bred animals?

We have epigenetic changes going on in conventionally bred animals all the time even in twins. How would you detect them? And would these subtle hazards pose actual risks to either the animals or to people consuming food from those animals? And if there were risks, how could you measure them?

(Slide)

So here is a little table that we pulled together that sort of worked this through as a theoretical framework.

The subtle hazard in the first column across is a change in gene expression that could lead to change in protein structure or function.

So the general risk to the animal, according to our framework, could be postulated as toxicity of some sort, from very mild to reasonably severe, due to aberrant protein expression. Protein can be an enzyme, you can lose catalytic activity. A protein can be a structural protein and you might have some kind of alteration in some --- as the result of that.

A hypothetical food consumption risk might be increased allergy to milk because you have somehow changed the presentation of a key milk allergen. Or changed nutrient content of milk because of a change in catalytic activity, you are no longer manufacturing the level of thiocin that you think you are manufacturing, for example.

These are the kinds of things we asked. I am not going to walk you through the rest because they are pretty self evident.

(Slide)

So how did we develop the methodology? Well, we went through a number of iterations. When I was first learning risk assessment I was told that it was an iterative process. I said, yeah, yeah, three months. Well, a year

later we are still refining the methodology that we are using and it really is an iterative process because data comes in all the way along and you have to change assumptions based on the kinds of things that you actually can observe.

(Slide)

We took a two-pronged approach to evaluating food safety. The first approach we named the critical biological systems approach. I will talk about that in a little bit more detail next. But it's based on the premise that a healthy animal is likely to produce safe food.

The second prong is the compositional analysis. And it asks whether food products from healthy animal clones or their progeny -- if food products from healthy animal clones or their progeny are not materially different from those derived from conventional animals, then they likely pose no additional risk.

If both of these requirements are met you can make a reasonable argument that foods from these animals could enter the food supply.

Now the thing that is important to note about this is even though it looks like these are two independent prongs, they are not. And they are not because of the underlying biological assumptions that exist in both approaches.

A healthy animal that is virtually indistinguishable from a conventional food animal is not likely to produce milk or meat of a compositional difference from a conventional animal. If everything is the same, then you expect the same out. It's nice to confirm that. It's nice to have the confirmatory composition data that demonstrates indeed that there is no material difference between the products of those animals. But please understand that these two prongs are mutually reinforcing.

(Slide)

So what is the critical biological systems approach? Well, it's mechanistically derived. It's HACCP-like in that it considers the life cycle of the animal in a systems approach. It accepts somatic cell nuclear transfer as a biological imprecise and inefficient process. We have a low rate of animals coming out of the SCNT process.

But, it allows for biological repair or correction just as every biological system has a capacity to do. That repair can be intrinsic or it can follow human intervention. We call that medicine.

Its cumulative nature allows for the incorporation of both favorable and unfavorable outcomes. So it's open to both positive and negative results. And it's a suitable framework for characterizing both animal health and food

risks.

(Slide)

And this is what it looks like. It started out looking as a very, very complicated wiring diagram. And we have trimmed it down to something a little bit more manageable. And it consists of basically of five developmental nodes. And the reason we did this was that remember we had about 100 papers we needed to analyze. Going through them paper by paper does not help you make a systematic analysis of the health of the animals.

But giving yourself slots to put information into from each of these papers allows you to cumulate and compare across different developmental nodes of these animals.

The first stage is a self cell fusion through fetal development, a lot of emphasis in the literature on these steps. And most of the papers that you will find in the literature, if you do your own search, will address this particular developmental node.

We have the perinatal development and functional period, which is the period immediately preceding and following birth. We have juvenile development and function, which is post-perinatal up to about to pubertal period.

Then we address reproductive development and function, which we put a lot of weight on, because the

reproductive system is so complex and so highly integrated that we felt if you had a correctly functioning reproductive system that likely the animal was in pretty good shape.

And finally we considered post-pubertal maturation which was all of the maturation processes that might occur simultaneously with reproductive maturation, but did not specifically address reproductive function.

As you can see from the pink and brown call outs, this also allowed us to identify points in the developmental process of these animals where we might have a food consumption exposure. So you can see this framework allows us to consider comprehensively all of the life stages of the animal that are relevant to both animal health and food consumption and allows us to cumulate data across studies in a systematic way.

(Slide)

As you know from looking at our executive summary, our draft executive summary, we were able to draw some interim conclusions on animal health regarding, based on the literature review using the critical biological systems approach.

As I said to you before, with a few notable exceptions, most of the information came in the first node of cattle. Several studies often cited --. Several of the

studies that are often cited address transgenic clones. And in some of these papers where we were hoping we would get a lot of information, because there were several score of animals evaluated, there was no individual identification of whether an animal was transgenic or just a clone. So we were unable to make that distinction. And, therefore, those papers became of extremely limited utility for us.

There are very few animals that were just clones as the result of this data set. And as we broke them into species, we realized that the database was not enormously extensive.

And often there was cursory information on the health status of non-neonatal animals. Again, because people are anxious to publish about their neat and new cloning technique and how good the efficiency is, there might be a throw away line somewhere in the discussion section that says clone 753 aged uneventfully, went through puberty as expected and gave a normal offspring. Well, that is not very helpful to determining what the health and safety of the animal is. But it is cursory information. You can't just throw it away.

(Slide)

So the next steps. What were we going to do with this data set? Well, we developed a wish list of information that we thought would be helpful in assessing animal health.

Like good scientists, good regulators, and good transparent participants in the process, we went and gave presentations to various professional society meetings and other public fora at which various members of the cloning community and interested other public citizens attended. And we had several conversations with several clone producers.

(Slide)

One of the things we decided should come out of that is this wish list. And the wish list basically said that what we would like to have are species and life stage appropriate comprehensive veterinary examinations and clinical measurements of blood and urine from these animals.

And we would like to have these veterinary exams and clinical measurements at several developmental nodes because we have constructed this lovely critical biological systems approach. And we thought if we could get some additional data it would help us look across the data in the literature and also evaluate what would get in hand.

And we also thought that it would be extremely useful to have necropsies of animal clones that had died prior to use. And whose deaths were not immediately attributable to normal events.

One of the things that I learned at CVM was that agricultural animals are not laboratory animals. You don't

get to keep your cows in a nice plastic box in a rack in your animal handling facilities. Cows live in barns. Barns have rails. Cows occasionally put their heads in the rails and hang themselves. That is probably not a cloning related injury. That is probably a cow related injury.

(Slide)

So we came up with, we went to various reputable animal diagnostic laboratories and came up with a list of the standard tests that are used to analyze blood both with respect to its chemistry and its cellularity.

And then we thought, well, you know, given this is the FDA, we have had some experience with controversial subjects, there are some things that people are interested in that maybe if we don't gather data on immediately, we should at least reserve some blood samples for so we can analyze later.

And in particular we looked at Serum IGF-I, we felt we would reserve a sample for. Not because we have any a priori biological reason to suspect that this is a risk. But rather because so much public attention has been called to it. And also estrogen for the very same reasons.

(Slide)

So back to our two-pronged approach. And let's think about the compositional analysis that we were looking

for. Again, just as with the animal clones we decided the regulatory requirements for foods from animal clones must be met or exceeded regardless of whether they are conventional or cloned animals.

So we would ask any of the foods to meet the requirements of the pasturized milk ordinance. any USDA inspection criteria, the Center for Food Safety and Applied Nutrition labeling requirements, and, of course, our Center's blood residue requirements.

And if we were thinking about the compositional analysis, we would ask that the constituents be within contemporary normal ranges for variability for that food product. In other words, it would probably not be appropriate to dig out a text book from 1938 that evaluated the composition of milk from Wisconsin cows and compare California bulk tank milk from 2002 to those values. That would not be an appropriate comparison.

And finally that the identity standard analyses would reflect the genetics of the animal that is being propagated. In other words, don't compare meat from dairy cows to meat from Angus for example.

And the outcome criterion that we would be looking for from this would be a statement that the milk or the meat would not be materially different from conventional animals.

(Slide)

So we ran into a little bit more of a problem here than we had with the data for the biology animals. And that was until this Fall. There were no peer reviewed publications relevant to SCNT animal derived milk or meat composition. There were none.

There are several reasons for that. One, very few clones have been bred, are old enough to be bred, and to produce milk. Very few. There is little impetus for the private companies who are doing this to publish the composition of the milk, even though we might ask them for it.

And, finally, meat composition requires sacrificing the animal. We called around to all of the meat testing laboratories that we could identify and asked if any of these analyses had been miniaturized to the point where we could use a punch biopsy for example.

And the answer was no. You needed kilogram amounts of meat. And at \$20,000 per clone, that is a lot of money to pay to sacrifice an animal. And then how many animals do you need to sacrifice in order to have a good statistical survey?

(Slide)

So once again, we divide that wish list. And you can see for the milk and the meat we decided that what we

really needed to do was to characterize the primary constituents of those products that would lead to a potential nutritional risk. So we asked for proximate, plus test vitamins and minerals for which meat or milk were a moderate to a major source. And you can see those listed.

And we had asked for fatty acid profiles, which again would be of dietary importance and would also, remember we said the two prongs are neutrally reinforcing. They are not independent. If you can go through this fatty acid metabolism and do all the fine steps that are involved then chances are you have got a well functioning animal.

We asked for a protein characterization. Not for exact breakdowns on each of the proteins because you don't eat meat and you don't drink milk for the full proteins that are there. It's for the amino acids that are there. So we had asked for an amino acid profile particularly concentrating on the essential amino acids.

And, finally, for milk, the somatic cell count just to indicate that the animal is healthy and see if we can move forward from there.

(Slide)

Well, lo and behold, coming out in this quarter's issue of "Stem Cell and Cloning", is a study by Marie Walsh and her colleagues on the composition of milk from dairy cow

clones that were described by Forsberg, et al, in a paper that we also used to look at animal health that Dr. Dubbin will tell you about.

They looked at 17 clones derived from five cell lines that were cows that were bred by AI. All right, so don't be confused here. The cell lines are derived from animals that were bred by AI, but they went on to make somatic cell nuclear clones from them. Two Holsteins and two Holstein Jersey process.

And, interestingly also, there was one female progeny of a bull clone, although they didn't specify the breed of that animal.

The comparators that were used in this analysis were approximately age and lactation stage matched animals. They were not housed at the same farm. And they were only softly breed matched. There were five Holsteins reared at one farm and one Brown Swiss cow reared at a second farm. All of these animals were fed different rations. Although the rations are not described fully enough so that we can make some attributions as to the effect they may have had on milk composition.

(Slide)

The analytes that Dr. Walsh and her colleagues evaluated looked in the milk, were total fat, nitrogen,

solids, lactose, PH, somatic cell count, again an indication of the health of the udder from the animals from which it came. An acid degree value, which is an indication of the rancidity or the off flavor of milk. Several key elements. Several fatty acids. And they looked at protein composition.

You will notice that some of those values, it's not your stigmatism, it's some of those analyzed are in bold. And that is because they coincidentally happen to fall on our wish list as well.

(Slide)

So here are the results of the Walsh study. All of the values from these animal clones and the one grand clone, okay, that was the daughter of a cloned bull, fell within either comparator or published ranges, with the exception of strontium.

And the only reason for that --. Or the reason for that is not entirely clear because there is no published range. There is only a single value. So if you have one value comparing it to another value doesn't give you very much information. When you look at the paper you will see that the strontium levels in the clones were lower than the published strontium levels.

(Slide)

So Dr. Walsh and her colleagues concluded that the

composition of milk from somatic cell cloned cattle was similar to that from non-cloned animals. And that the differences between clones and comparators were likely attributable to differences in breeds, diets, or housing.

It's important to remember the number of animals in the study is relatively small. But the results are entirely consistent with the health data that you will hear about from Dr. Dubbin.

(Slide)

Next I want to go very quickly through the mouse literature. Remember we said we were going to look at model systems where we had insufficient information and rather than including that in our data summary, I will tell you a little bit about it now, and include it in our methodology discussion.

(Slide)

Mouse literature in many ways is very similar to the livestock literature. It tends to focus on interesting outcomes rather than on overall health surveys, for the reasons that John discussed, there is a publication bias out there. It may provide insights into the underlying biology, however, of the overall cloning process.

Because mice have relatively short generation times, these studies may provide us clues to reproduction,

longevity and agents related phenomena. And it's interesting to note that some of the anomalies that we have noted in mice are similar to the anomalies that were noted in livestock. Others are very different.

So like every model system it's very important to interpret the results with care. This is a model system. It is not a direct representation of all of the other systems.

(Slide)

So what do we know about mice. Well, similar to livestock clones, mice often have large abnormal placentae. I am jumping the gun a little bit on what Dr. Adams and Dr. Dubbin are going to tell you, but trust me there are some large abnormal placentae in cloned animals. Some of these mice also have perinatal respiratory difficulties either arising from cardiovascular defects or birth related phenomenon.

There are, however, some distinctive phenomena that also have been observed with mice. In one laboratory, one strain of mice that has been generated using one cloning technique, animals have shorter life spans, significantly shorter life spans than their donor animals.

Those animals appear to die from various kinds of liver pathologies. Again, that however is limited to one laboratory in strain out all of the data that has been

observed. In another laboratory some of the mouse clones have a very unique obese pre-pubertal phenotype that is reproducible in that laboratory using that donor line.

(Slide)

So what insights do we have from the physiological mechanisms that may be perturbed in all animal clones from the mouse model system? Well, we know that placentation is affected. Without going into details there have been a series of rather elegant studies that have asked the question are these changes due to genetic modifications or epigenetic modifications. When the entire report comes out you will see that this group of scientists has done an elegant job of demonstrating that these are epigenetic changes and not mutational effects.

That there is fairly rapid resolution of perinatal fragility, as Dr. Dubbin will describe to you in the next half hour. And the most important thing that the mouse data has taught us is that anomalies noted in clones that are specific to cloning, in other words, an animal that may have a genetic defect may propagate that defect.

But if there is an anomaly noted that appears to be cloning related, such as the unique obese phenotype, that phenotype is not transmitted to progeny. Reproducibly not ever in the publications.

So predicative interspecies extrapolation for specific endpoints or outcomes should be attempted with caution. I think what we go to the mouse studies for is some good understanding of what the underlying biological systems that may be involved are. But to extrapolate from any particular endpoint from mice to livestock is probably inappropriate, just as it is inappropriate to extrapolate for example from goats to pigs.

(Slide)

So what happened next? We are stuck with this set of papers that has spurious, or not spurious, but very cursory information about animals as they age. Don't really have a whole lot of physiological or biochemical data. We are going out and hawking our risk assessment across the country. And lo and behold, one company stepped up to the plate. And I would like to thank Cyagra Incorporated for supplying us with an extraordinary data set.

(Slide)

This data set is the reason why you are reading the executive summary and not the entire risk assessment right now. Cyagra made these data available to us in the Summer of 2003. It's important what they did basically was to go out, try to identify every clone that they had generated.

And as a snapshot in time, if you are an

epidemiologist you can think of this is as a cross sectional study and not a longitudinal study. Assayed the health and took blood samples on all of these animals. It took them long enough to do this, but they were able for a very small subset of animals to get data on both the neonates and those animals a little bit later.

They shipped us electronically that entire data set, including the direct evaluation of the clinical chemistry from the Cornell Animal Health Diagnostic Laboratory. And said, go to it. It's publicly available. Do with it what you please.

So that is what we did. We analyzed it every which way from Sunday. And what I would like to tell you about, or what Dr. Dubbin will spend most of the time talking to you about that data set. Because it is the most comprehensive and complete analysis of the health of animal clones.

Unfortunately it's only limited to cattle, and that is their business decision, we don't have anything to say about that. But, that is the way it goes.

In addition, we have received other data from other clone manufacturers. It tends to be on specific endpoints and may be on different species. With apologies to those clone producers, we have not incorporated it at this time. But we will in subsequent iterations of this risk assessment.

So we decided to move forward even though we knew it would delay the completion of the appendices and the decent proofreading a document of 300 pages in length would require.

(Slide)

So, finally, let me wrap up by telling you what the rules are that we were choosing to apply to our risk assessment. Again remember we have the initial criteria that the animals appear normal and healthy. Those that exhibit gross abnormalities or disease are culled and do not enter the food supply. This is not special for clones. This goes for food we eat every day.

Meat and milk appear normal and neither exceed federal, state, and local standards. Again, nothing special for clones. Same requirements that we have had for other food animals.

(Slide)

We did something a little different. We decided to make our biases transparent. Now there is no such thing as going into an analysis without a bias. People can tell you that that is the case, but that is not true.

So we decided that we would take the two extreme biases that could be taken for clones. And we would bound the risk face in which we were operating using those two

biases. And by clearly identifying what those biases are, we could be transparent about where the data was taking us and how much confidence we would have in our conclusions.

So our first hypothesis is the more liberal interpretation that assumes that clones are exact biological copies of the donor animal. And that all you need to confirm that are confirmatory findings of health and food product comparability to indicate that no additional risk is posed by the consumption of these food products.

The opposite face, the other bound on this, is that animal clones may appear to be biological copies of the donor animal. But subtle hazards may have been introduced by the somatic cell nuclear transfer process.

To avoid additional risks above those posed by the consumption of foods from conventional animals, comprehensive health and compositional data are required to demonstrate that the animals are healthy. And that food products derived from them do not differ materially from those derived from conventional animals. So those are our biases.

Again, as was told at the beginning of these assessments, this is risk assessment. This is science only. These biases are scientific biases. They are not morale or ethical biases which are more appropriately handled in the risk management component of this overall process.

(Slide)

We evaluated the weight of the evidence for animal health and food safety based on the literature and the data that had been submitted.

(Slide)

We will state our conclusions regarding risk using the following criteria. Any biological assumptions that we implied. Remember we said it was relatively value free, but there were assumptions used in risk assessment. The empirical evidence that we evaluated. The consistency of observations among the animals of that cohort and across other cohorts as well.

The degree to which model systems apply to that particular endpoint that was being evaluated. And the consistency of that model system with the data that we were evaluating.

We would state our uncertainties associated with any preliminary estimate of risk that we might make. And then make an overall statement of the confidence that we would have in that estimate.

So what you have here is a fully transparent decision making process that identifies the two bias perspectives that you can take, where the data that drove you with respect to that risk finding exercise, the uncertainties

that were still associated with it, and our confidence in our estimates of risks for that particular endpoint.

(Slide)

Now it's important to understand what the limitations on any risk assessment are. This is a qualitative comparative risk assessment. We are not going to come out with a number that says meat from animal clones is then many times more or less risky than conventional meat.

What we are going to do is compare these animals to comparators of known or inferred safety. And the known or inferred safety that we are comparing them to is the food that we eat every day.

The strongest conclusion that you can get out of this kind of a risk assessment is likely to be as safe as. So what does that mean in the context of animal health and food consumption? When we say a finding as safe as for animal health, that means the cloning process is likely to be as safe as other assisted reproductive technologies. That is our comparator of known or inferred safety.

For food derived from clones the finding of as safe as means that food derived from animal clones is likely to be as safe as the foods that we eat every day.

(Slide)

Finally, we made some recommendations to decrease

uncertainties. There are always uncertainties associated with every bit of science. Risk assessment, as I said, is an iterative process. We can always call for more data. We can also be paralyzed by analysis.

So one of the things that we need to do is to, and that we will ask for your opinion on, are the relative merits of additional data. And so that we can then take those recommendations forward to risk managers so that a transparent statement of risk tolerance can be made.

(Slide)

So we have been promising you this risk assessment. We are still going to promise you. And the last little teaser here is what is the overall structure of the risk assessment going to look like when it finally comes out.

We want this document to be accessible to the entire public, from the scientists to the layperson. To that end you have already seen the draft preliminary executive summary.

The next chapter in the risk assessment will be a technology overview that will review assisted reproductive technologies as they are currently employed in the U.S. agriculture. A little bit about how long they have been around. How much they are used, and what they are actually like.

There is a short primer on hazard, risk, and cloning, most of which you have heard today. A chapter on risks to animal health. A chapter on food consumption risks. And a final closing chapter with overall conclusions. There are several appendices which you see listed on the right hand side of that slide.

There will be a comprehensive bibliography, including all of the raw data that Cyagra submitted. Raw data. Individual animal numbers. And a complete glossary so that anybody who is reading this document doesn't feel that they are stunned by techno babble.

(Slide)

This risk assessment we believe has a great deal of value to us as a regulatory agency, to the scientific community, and to the lay public. It's a logical framework that is tailored to a specific question. It's a systematic analysis of available data that have multiple uses.

It identifies clearly data gaps. It performs weight of evidence evaluations that accommodate data, biological assumptions, biases, uncertainties, and the degree of confidence that we have in the conclusions.

And finally we believe that this gives all of the stakeholders involved in the process a degree of transparency that we may not have seen before. And this preliminary

presentation of the executive summary is the first step in that transparent process.

(Slide)

Finally, I would like to acknowledge all of the people who have worked on this team. Without them, none of this would have been possible. And with them we have, I think, come up with a unique product.

Dr. Amey Adams, you will see soon. Eric Dubbin, who has been involved in things. Kevin Greenlees, who has been actively involved in the preparation of the final document. Dr. Barry Hooberman, from our risk assessment group. Dr. Wendy Jones, John Matheson and Christina Musgrave, our consumer safety officer without whom none of the data management would have been possible.

And finally I would like to thank our reviewers, Dr. Hungerford. Gail Schmerfeld. Dr. Sherman. Dr. Schoenemann. Jody Fleming, who was a summer student with us from Rutgers. And many, many others at the Center and outside for all of their help.

(Slide)

And finally to Ray Page from Cyagra for his openness, continued availability to answer any questions about his data set. And to other producers whose data we have not yet included.

And for photo credits, of course, we would like to thank Cyagra, Nexia, TransOva, I think Jodie Palmer is here. ViaGen. Mike, thank you very much. And Jorge Piedrahita. And of course Bob Wall, you get thanked twice because you didn't end up on the slide. Thank you very much for your attention.

(Applause.)

Summary Data from Animal Clones - Part I

by Dr. Eric Dubbin

DR. DUBBIN: Thank you, Larisa, for that overview and teaching us all something about risk assessment and how this process is being evaluated. My name is Eric Dubbin. I am a large animal veterinarian and I am a member of the ruminant drugs team at the Center for Veterinary Medicine, Food and Drug Administration. Just one second.

(Pause.)

(Slide)

This is a review of the critical biological systems approach and each node that we used as developmental landmarks to couch our discussion in. The first node, cell fusion through field developments. It's before the calves are born. Then perinatal development and function around the time of birth. Juvenile development and function.

Then when the calves go through puberty and have

reproductive development and function. And finally post-pubertal maturation where we see how well the animals age as adults.

(Slide)

The overview of my presentation is we are going to do a species by species evaluations. We are going to talk about key outcomes in the critical biological systems approach context.

We are going to emphasize the data as it corresponds to the developmental node and how it relates to animal health risks and food consumption risks. We will also have a more detailed presentation of the Cyagra data, which is the largest single data set and our most detailed data set.

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The first node is cell fusion through field development. This is the period of highest risk for the developing clone where we can see failure for the embryo to divide or implant. Defects in reprogramming. Problems with placentation. There are problems in this node throughout all the species we have evaluated.

The percentage of surviving this particular node is low and the data that we have are limited for further assessment, but the data do help set the stage for the next

node.

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With that I would like to talk about specifically about bovine clones in the framework of the critical biological systems approach.

(Slide)

When we look at bovine perinatal clones what we see is that there are really few laboratories, lots of data, but few laboratories with the key studies. Another issue is that many of these studies discuss transgenic clones and not just clones alone. And if you remember we discussed that transgenic animals were going to be left out of this assessment.

So the number of actual "just" clones is relatively small, about 50 or so. Most of the information on overall health is somewhat cursory, or as Dr. Rudenko mentioned earlier, the passing discussions of the animals were healthy after they got the information they wanted.

There are few physiological or biochemical studies with lab data and blood data. And one thing we do see in bovines that the large offspring syndrome is quite common. Large offspring syndrome, for those of you who don't know, is a collection of findings where the calf, the neonate, the newborn, is larger than expected for the breed.

There may be some placentation problems occasionally. Parturition may be delayed. The calf is unthrifty. These calves might need support by nasal gastric or oral gastric feeding and respiratory support with --- oxygen and such. Most of these animals survive and Dr. Adams will discuss this condition in more detail later and you can see my bottom bullet there is not showing up very well.

(Slide)

What we see over and over again is that the newborn clones are particularly fragile in the first few days. There is a higher incidence of death early in the development of this technology. But we do see an improvement in success rates as the technology itself advances.

In clones we see no qualitative difference relative to other assisted reproductive technologies. Qualitating meaning the types of problems. We do, however, very clearly see an increased frequency of these problems. Most commonly LOS, which I mentioned previously. These calves tend to be a little higher birth weight than their age matched comparators.

And you will hear the term age matched comparator over and over again because it's important that when we use a reference, that the reference we use is appropriate and age matching comparators or comparing animals of similar age,

similar breed, similar diet, similar farm background is very, very helpful for a meaningful comparison.

We do see more common cardiovascular malformations more commonly. We will see respiratory problems and flexor tendon contracture. Understand that elevated birth rates, cardiovascular abnormalities, respiratory difficulties and contracted tendons are not unusual to cloned animals.

(Slide)

So that is the perinatal summary of the literature. The next node I want to talk about is juvenile development and function. This encompasses the time in and around weaning, depending on the species because different species are weaned at different ages.

(Slide)

What we find in the juvenile period in cattle is that initial instabilities that were seen in the neonatal group tend to resolve. They tend to lessen. We see problems less commonly in this group of animals. Of all the literature, the 500 papers that Dr. Rudenko talked about, the total number of clones in all of those papers were about 100 animals. And in those 100 animals, only three deaths were reported in what appeared to be otherwise healthy animals. So the numbers are not large.

In one study there was a description that growth

hormone and IGF-I levels were lower in the cloned animals than they were in the control animals. The growth and general health was reported as normal.

And another study on behavior of cloned animals described their behavior as normal and that their behavior actually resembles the donor. The dam had, you get a personality type, and these clone offspring had a similar personality type.

(Slide)

Continuing in the bovine juvenile node, we see a description of one cloned animal with lymphoid hypoplasia that died at day 51. Again, this cloned animal with this problem we do see conventionally bred animals with lymphoid Hypoplasia as well.

In a study of Japanese Black Beef clones, of the 12 clones surviving the perinatal period, which is a previous node, all of those 12 were healthy and normal up to about a year.

In another study there were four clones derived from ear cells of a 17 year old Japanese Black Beef bull and the paper reported that they were all alive and healthy at ten to 12 months. That the veterinary exams, growth curves, and 30 day blood parameters were normal, although no data were provided.

(Slide)

Continuing in the same node for cattle another study reported on 21 healthy appearing clones. And they took physiological measurements. These calves had an elevated body temperature for a month or two. These body temperatures were not responsive to non steroid anti-inflammatories, with no abnormal blood work, per se. We can be pretty sure these animals did not have some kind of infection causing elevated body temperatures.

Some of the blood parameters or analytes that were analyzed were initially unstable. They showed lots of variation and that variation resolved within a few weeks. The basic clinical chemistries were normal. And they also ran some hormone levels. IGF-I, IGF binding protein, leptin, insulin, post prandial glucose. Those all were reported to be normal.

There were some differences between the clone and the control calves with their level of thyroxine, leptin, and IGF-II. But the paper reported that those differences resolved in two weeks.

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In summary, from this node of juvenile development, we do see physiological instabilities. Fewer in this node than the previous. And those from the previous one tend to

resolve by the conclusion of this time period in the clone's life.

The lab results that were generated showed an appropriate response to growth and development. There are certain analytes that animals will, well all animals including me and you, will have differences as animals grow, as they grow. For example, calcium phosphorous and alkaline phosphotates, which I will discuss later and you will see later. These are growth related analytes. And animals with elevations of these are generally beyond growing animals. And we will see more of that.

And obvious physical anomalies, things that looked abnormal were clearly identified as abnormal. So, in summary, normal and healthy animals behave and appear to function normally and are indistinguishable from their comparators.

(Slide)

The next node is after these animals go through their juvenile development they then go through puberty, God willing. That is what we are looking for because we want to breed these animals. They are clones with superior genetic merit and their job is to produce offspring with superior genetic merit. So the reproductive system is important.

And as you might be aware, the reproductive system

is an extremely complex set of interactions. And we made the assumption we considered that if a clone was able to successfully breed, that is it showed breeding behavior, and actually reproduced, which is to calve or develop offspring, that that would demonstrate that in the process of cloning the animal still has maintained appropriate control of this extremely delicate and sensitive process.

Success at this node indicates to us that the clones are genetically well integrated because this process, this subtle delicate complex process, is functional.

(Slide)

With that being said, the data that we have on the reproductive node is quite limited. There might be a cursory mention, as Dr. Rudenko said previously, a cursory mention of normal activity at the end of the paper really designed to look at something else. And they do have this information they included, but it's not detailed and comprehensive.

There is a paper where there was explicit evaluation of bovine clone reproductive function. And this one paper reported that puberty occurred somewhat later in the clones at 314 days on average compared to the conventionally bred counterparts at 272.

These animals, the cloned animals, had a higher body weight at first estrus of 336 kilograms versus the

controls of 302. The authors discussed that there is no difference in the cycle length, the average cow cycle is 21 days, follicular developments and the hormonal profiles like daily luteinizing hormone, follicle stimulating hormone, E2 is estrogen and P4 is progesterone. These were similar between the two.

It is important to remember though that this nice data set really centers on four cloned cows. So we are talking about four animals. The bottom bullet, which is still readable, three of the four clones were pregnant post artificial insemination. And four of the four controls were pregnant post artificial insemination. The number of inseminations wasn't reported. But artificial insemination, three out of four, is really not that bad.

There was another report of some Holstein heifers that were cyclic by ten to 11 months of age, which was in the normal range. We didn't include that on the slide because these animals, some of them weren't transgenic and we decided we are not going to include transgenic discussions in this. But, the fact that that was in the normal range is interesting to me.

(Slide)

There were more reports, again, these reports, more of passing mention of the reproductive issues. In one five

clones were healthy and normal and described as normally cyclic at one year of age. Cyclic means showing signs of estrogen, showing signs of heat.

Our clone named "Gene," a bull, was reported as being healthy, fertile and having sired calves by artificial insemination and in vitro fertilization.

Another report of a clone bred via artificial insemination, rather, conceived and delivered a calf described as normal. And another paper described two Holstein clones in an abstract. The abstract mentioned that the first post partum ovulations were delayed. That they had two follicular waves, two per cycle, which is within the range of normal. And these animals calved normally.

(Slide)

So, in summary, based on the data that we have, or rather on the review of the papers available and the literature, we see that clones appear to develop normally. That puberty was reached at a slightly delayed stage of life, you know, some larger body weights and by days, slightly delayed. But the reproductive function that was observed and measured was described as normal for how it was measured.

(Slide)

The final note that we have and that we have reviewed in the literature is that of post-pubertal

maturation. Concept of lifespan. And that is an important concept because we all know that Dolly died, was considered at a younger age than we would have expected for an animal that was pampered.

But the concept of lifespan for food animals is different than it -- oh! Also, and Dr. Rudenko discussed the mouse model. The concept of lifespan in food animals is different. And this may be a review for many of you, but for those of you who don't understand or aren't familiar with this, food animals come really in two types. There are brood animals and there are market animals. Brood animals for breeding and market animals for consumption.

Market animals are raised until they reach their market weight. They are then slaughtered for food. This is about at 18 to 24 months for cattle, and six to eight months for swine.

Brood animals are breeder stock. They are designed to produce offspring year after year after year, as long as they are capable until they become either infertile or develop a disease or lameness where they can no longer perform.

Left by themselves, cattle, pigs, sheep and goats, could probably live for up to 15 to 20 years, although they are usually culled well before that time.

(Slide)

The technology is relatively new and few bovine clones have reached an advanced age to have information on longevity. Also, in the literature we have no reports of sudden abnormalities arising.

There is a report that a bull named "Second Chance" --. Hill reported that Second Chance as a neonate had diabetes that was treated. The diabetes resolved. And the animal is now three years of age, has normal body weight, growth, behavior, and as a bull, all important semen production.

I am at the 10:30 mark. What do you suggest I do? I mean this might be a good time for a break. I am about to go into the next thing.

(Slide)

The next section, a little teaser for you. My next part of this is when I actually review the actual data, cattle numbers, health records, lab data. And it's pretty interesting. I would like you all to be fresh before I get into it. So, it's time to break. We will see you all at 11:00 o'clock. Whatever the agenda says.

(Whereupon, a recess was taken.)

Summary Data for Animal Clones - Part II

by Dr. Eric Dubbin

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DR. DUBBIN: This is what we were waiting for. In the Spring of 2000, we encouraged producers to publish data on the health of clones. Back in the Fall of 2002, we presented our draft risk assessment methodology. And then in the late Spring of 2003, we had an influx of new data from the Cyagra company.

The Cyagra company clones cattle, or at least those were the data provided. And in the data set were physical exams, medical records, and this part about the laboratory data is key. These were systematically collected laboratory data. Data collected on all animals based on the calendar, not based on diagnosing a disease.

(Slide)

Since we received this set of clinical data, we reviewed them in the context of clinical medicine. And clinical medicine uses something called the problem oriented medical approach.

The approach is contingent really on an animal having a problem. And you look at that problem and you take its history. And then you examine the animal to determine if you can -- the physical examination findings will tell you anything more about, tie the history and the complaint together so that you come up with a diagnosis.

This is also somewhat of an iterative process. We

have all these problems and you are not sure what it is yet, so you then run some confirmatory tests. This is clinical pathology. So-called blood tests, chemistry, electrolytes, the blood cells, and urinalysis.

And you use these lab data to help bolster your argument for what you have done in your physical exam, your history, and your chief complaint. That is the model under which medicine is practiced.

The point of this slide is that you must understand that lab work by itself is not a free standing item. It is the context of the animal that you use to judge the relevance of the lab work.

(Slide)

So clinical pathology, which is a very fancy name for "lab work" complements the physical exam. It assists in the diagnosis. And lab work has its downside, I shouldn't say downside, but limitations would be a better word to put it.

The reference ranges that you use to determine if an animal falls in the normal category are based on a population that the lab uses for healthy animals. They take the lab values from health animals. They take the mean at plus, minus two standard deviations and come up with a list of normal values with 95 percent confidence. Meaning five

percent of the values you have may be okay, but out of the range just based on chance alone.

So you can't scrutinize the data that every single thing is out of range has a whole lot of relevance per se. Also what was the lab's reference population . Many labs use healthy adult animals.

Another issue with clinical pathology is the concept of artifact. Artifact is an unexplainable error that is caused by, for example, an error at the lab, an error in collecting a blood sample, putting it on the dashboard while you get a cup of coffee, then you take it away. Artifact happens. Not that I have ever done that.

(Laughter.)

But, again, the point of this slide is to remember that clinical judgment, the context, is still required when reviewing lab work.

(Slide)

So the data set that we received had 74 samples from clones. That is split up into ten neonates, defined as less than 24 hours of age. 46 calves from the one to six months age group. And 18 calves from the six to 18 month group. For a total of 74.

At the neonatal stage, seven calves from that stage survived and we received blood work at the one to six month

stage too. So there is a repeat of seven calves. From comparators, we had 17 neonates, 47 one to six months old comparators, and 21 six to 18 month old comparators. These animals were age matched and very helpful for a reference point of view.

(Slide)

Again the data set discussed mortality. It discussed physical exams. It had actual veterinary exam forms. It discussed clinical picture. It discussed surgery. We saw some umbilical problems, which I will talk about and describe in detail. And discussed how many animals were for cull.

So before we look at the clinical pathology data, we want to take a look at what appears, what I would call the big picture. What all was going on with these cloned animals.

(Slide)

134 cloned animals had data on them submitted to us. Of these 134 clones, 28 of them were listed as being stillborn or having died or euthanized by 48 hours of age. 11 calves were described as having died from after that stage too, and there is typo, that is actually one and a half years, or 18 months --- were followed up.

The split of the 11 calves that died after that

point, eight of them died in the first month. Three died from one to six months. And none died after then. You will see that the numbers don't necessarily, the numbers on this slide add up. But, the numbers don't necessarily add up everywhere you look. And the reason for that is we received the data in two sets.

The first set was scrutinized very carefully. It has all of the lab data. And that is the first 74 calves that were on the previous slide. We have since received subsequent data on 60 more calves and it's too good not to -- it's too good to have this, not to use it. But we can't necessarily put them all in the same context. We don't have the same level of detail on the last 60 as we do on the first 74.

(Slide)

So in further discussing the mortality listed in the data set, of the 28 that died in less than 48 hours, 11 were stillborn, 12 were euthanized for abnormal development, defined loosely as sort of different problems, and contracture means contracted tendons, or bent legs.

Two were actually infected with rotavirus diarrhea, a very common cause of diarrhea in calves. And two animals succumbed to that. Three died from unknown causes and their clinical picture is described normal. One had a thickened

placenta and pericarditis. And one had a moist umbilicus and was depressed.

(Slide)

For the calves that survived over two days, those 11 calves, three of them had umbilical problems and sepsis from those umbilical problems. Three of them had gastro intestinal problems described as bloat adhesions. And the rupture there is, evidently this calf ate some wood chips and it had a bad reaction to that. And that is hard to attribute to cloning.

Three of them had circulatory problems described as failure to, various different types of circulatory problems. Failed to convert from fetal to neonatal circulation and such. One animal had contracted tendons and was not responsive to therapy. And one had an accidental trauma. As Larisa described in the previous talk, it's hard to attribute trauma to cloning.

(Slide)

So now we look at what kind of physical exams did we have in the data set. And most of these, well these physical exams were submitted with this set. And described 11 clones with musculo skeletal abnormalities.

Of these 11 clones, nine of them were described as contracted tendons and these animals responded to therapy.

One was described as having thick withers, which is the shoulder blade area for those of you don't know, an enlarged carpus, which is the front knee, and this leg deviated laterally, which means it stuck out. And she was eventually culled.

And you will see this calf over and over again, because there is lab work associated with it. And it will be mentioned, so you will get to know her ear tag number by the end of this, I am sure. And the other musculo skeletal problem was a dwarf with frequent bloat.

One clone was having described as having early mammary development. And she was about four and a half months old. That is a little early for a calf to have mammary development, but I can tell you that I have worked with heifers for a long time and sometimes that just happens.

Two calves were described as having harsh lung sounds. Three bull clones were described as having a retained testicle, which is, the term for that is cryptorchid. And we thought this is awful curious. Maybe this causes that.

And we further scrutinized the data. We found it was all from the same donor and seemed to be some genetic link there and that is consistent with what we think of in clinical medicine.

And one calf was described as having a cardiac arrhythmia. How often do you have cardiac arrhythmia in calves in the general population? I don't think a whole lot of calves are auscultated or listened to routinely on a production operation, so it's hard to get a feel for that. It's not common, but I have heard it myself.

(Slide)

One of the health issues that we see with this data set and we have seen consistently throughout previous ones is that there are umbilical problems. 41 of the 134 calves were described as having umbilical difficulties. Bleeding, infection, adhesions. Two subsequently had cases of pyelonephritis, which is an ascending bacterial, I shouldn't say it's ascending, but it is a bacterial infection of the kidney.

Of these reported 41 problems, 29 of these calves required umbilical surgery. The extent, whether it's umbilical extrapolation, removing an entire umbilicus, or simply a repair of an umbilical hernia, we don't have that kind of detail.

Miscellaneous health problems, we talked about the rotavirus. I have talked about the GI problems. The failure to transition to fetal circulation and hypoxia. And the two culls.

(Slide)

Now we have these actual blood. We reviewed the general clinical picture. What kind of problems are we seeing? We have attribution of each problem with ear tags so we know who is doing what. Now we have lots and lots of blood data. How do we organize them? And how do we decide what to compare them to?

(Slide)

This chart is a little busy, so I will walk you through it. We took data from three different populations. That is the clone, the age match controls and the Cornell Reference Lab.

We then compared individual analyte values from one population with the range in the other populations. Counted the number of analytes that were outside the range and made the comparison that way.

So, for example, let's look at the top row. For the six to eight month old group, for clinical chemistry, ignore chart number. That is sort of internal. 75 percent of the clones had their values within the range of the reference range. So we would call that a 75 percent agreement, loosely.

On the next column we compare the clones to age match comparators, and you see that there is 99 percent

agreement. 99 percent of the clones have their blood values within the range exhibited by the age match comparators. And we have actual raw numbers for you.

Out of 592 total blood samples, or total values available, 586 of the cloned animals' values were within that range, which is a -- that is more than you would expect by chance alone.

And the final column we compared the comparator population, these are the non-cloned animals, the regular old calves. And compared how they stacked up against the Cornell reference range.

You can see that there was a 73 percent of the comparator, regular old garden variety calves, where their ranges were within the Cornell range. So you can see that the first and second column are almost identical, which is that there is equal disagreement of the clones' comparators to the reference range. But a very high amount of agreement with the clones and their age matched comparators.

That tells us that we need to be comparing these calves to their age matched animals. That is how we came to that conclusion.

But this chart illustrates something else that became evident as we were reviewing the data. If you look at the neonates, and that is the bottom row, and let's just take

for example the hematology, which is the very bottom row. I would like to thank Joanne for fixing this slide, because I couldn't make this point without it.

That if you look at the hematology in the middle column, right there (indicating) that 90 percent of the clone values were within the range of the comparator values. That is pretty good.

But as you go up the column, you go to the next node, one to six months, you see that 96 percent of the clone values are within the range of the comparator values. And as you continue up you see that as, what should we call them, six to eight months, or almost adults, market age or getting close to market age, that there is almost 100 percent agreement.

So the other conclusion we can make is that the older the animals get, the more stabilized their blood work becomes.

(Slide)

So now we have decided what we are going to compare and what we are going to measure. Now the question is how are we going to present this? How are we going to analyze it? What is going to give us a good visual, quick view, and it will be something that is concise so that you can fit it on one page, but it has to tell you something.

(Slide)

We came up with this approach. This demonstrates how we organized the data to get an overall view of the sameness versus the differences. Across the top, we have animal ID. That is an animal ID that we attributed to the animals. We kept their actual identities or ear tags to protect the innocent, or whatever. We didn't want them attributable to that.

So, across the top are the CVM's, our animal identifier. The first column lists the analytes that are measured, hematocrit, hemoglobin, red blood cell count and MCV, mean cell volume, and so forth. And then each black square indicates that for calf number 24, this clone's value for hematocrit was within the range of the comparator. And when you look at -- so that is what the black square means.

What the gray square means is that it is outside the range. Because we were strict. Boom. Inside/outside within point 01. Whatever it is. If it was outside, it was not going to be a black square.

But some of these were so close. You know, if you have, let's say, a glucose of 40 is the low, you have a glucose of 39, you are going to make that a huge issue, or is that within --.

So we said if something is within ten percent or

within from a practitioner's standpoint, within clinically close enough, we gave that a gray box, which still means we didn't ignore it, but we didn't give it the same weight as something that was truly out of range. Those are the gray boxes.

Things that are out of range and obviously abnormal, this would be an elevation, this would say that calf number 108 had an elevation of its red blood cell count. And then down arrows would be, that is compared with comparators, and that this calf 108 had an MCV lower than the comparison population.

Asterisk are missing data. X's, which you will see in coming up slides, are presumed artifact. We talked about artifact at the beginning.

If you look at the column on the far right, that is a summarization of all the calves. How many had hematocrits out of range? Zero out of 18. How many had hemoglobin out of range? Zero out of 18. RVC's out of range. The term out of range doesn't really specify above or below. It's just not a square.

And then along the bottom of the summarization is for calf number 24, for example, how many analytes did she have out of range. How abnormal was she? What kind of issues was this animal having? If you look, let's say we

look over at calf 108 again, two of her 17 variables measured were out of range.

When you look at this slide, what we see is that of, and I did a little math last night. I actually did it long ago, I just reconfirmed it. 294 boxes, 294 values to compare. Three arrows are out of range. That is 99 percent similarity between the cloned population and the age matched comparators.

If I was to show you a box of say when we compared it to the reference range, you would see all kinds of arrows and fireworks and things like that, because there just wasn't a good match and it wasn't an appropriate comparison.

(Slide)

So what questions do we want these data to answer? Generally, are these clones and their comparators mostly similar or are they mostly different? And if they are different, what are those differences.

Further, how do these animals respond to internal stimuli like stress and growth and developing immunity and you know growth and things like that. Or versus external stimuli like infection or heat or things.

Can these animals respond similar to their age matched comparators? And do the blood tests give us any predictor. Is there some sensible blood test that we could

run that tells us, that predicts the future of this animal?

(Slide)

We did notice some trends. The first trend is that growing animals, well I will just call it what it is. We saw an age appropriate response in the growth analytes. Growing animals, both clones and comparators, have elevations compared to our standard.

Remember we are not going to use it, but it's still instructive to determine, you see an elevated calcium level that is very high. You say, oh, my God, what is the matter with this animal. Well, you find you are looking at a reference range from the lab and not for the age matched. And if you are age matched, you say oh, they are the same. Well, that is because clones and controls both respond to the signals for growth by increasing alkaline phosphates. Increasing their calcium. Increasing their phosphorus.

This indicates that the animals' metabolic, both bone growth pathways are normal. That they are synthesizing Vitamin D. A functioning kidney. A number of pathways that are responsible for this are functioning.

(Slide)

The second response we see is an age appropriate response in immunoglobulin. Immunoglobulin is the prime component of globulin, which is on the chart. That is an

analyte that is measured. And it's also a big word for antibody.

So we see that young calves, both clones and controls will have lower globulins than their adult comparators. That is because young calves haven't started producing antibody yet. They are dependent on the antibody from the colostrum that they consume.

And as the colostrum wanes, their own body has to produce immunoglobulin and we see in both the clone and the controls that they both do that appropriately. So as would be expected for animals of this age group, we see elevations, age appropriate elevations of immunoglobulin.

And to review the data and to actually see that light come on, you go, wow, that is kind of neat. I wouldn't know what to expect.

(Slide)

So now I am going to go into essentially a blow by blow comparison of the neonates, the juveniles, one to six month, and the pre-pubertals of the six to 18 month. Comparing clinical chemistries and the hematologies.

This is a little -- well, I will just get to it. We have ten live cloned neonates. 17 comparators in this chart. Okay. This chart demonstrates a 92 percent agreement. That is 92 percent of the clones' values were

within the comparator range. That is actually, I stole that from the slides previous where I discussed with you the numbers it was based on.

If you look at the chart, I will try to make this fun. But, you will, if you go down this column (indicating) we are looking for big numbers. There is a big number. Boy, nine out of ten AST's are low. We see GGT here. This is a typo. For those of you have the actually things, that is actually six out of ten. Okay.

We see also the cholesterol is low in four out of ten. That iron has one low and one high. Two out of ten out of range. And then hBA-random is bioacids, which is liver, a measure of liver function. And we see here that there are six out of nine. Nine, because one is missing.

So what does all this mean? We know that AST, cholesterol, bioacids and GGT are often elevated in cases of liver disease. What does a low GGT mean? Or a low AST? That is not entirely clear. There is some discussion that since colostrum is high in GGT activity, that a low GGT may have cholesterol issues. Well, then I would look to my globulin and I see my globulin, which is antibody from colostrum, that globulin is right there. My God, they are all normal. Normal globulins.

So I looked into it and found that there was one

control calf that had extremely low globulin. So that could have just been a spurious finding. And that is one of the limitations of this type of comparison. Spurious finds can affect the limits of what is considered normal.

So that is a summary of the out-of-range analytes. Mostly liver related. Some of them may be colostrum related. I can speculate as to why these liver values are low, but I won't do that. This isn't the place. You are going to have to wait until the book comes out.

The calf here, 43, we see she has four analytes out of range. Low bioacid, low cholesterol, like they all seem to do. And low chloride. This is one of the calves that died of rotavirus.

Calf 79, you will see her later. In fact, you will see seven of these later because we have two time points and I will wait to discuss them then.

(Slide)

And hematology we see 90 percent agreement between the clones and controls. 90 percent, still pretty good. Not as good as it gets as they grow older.

If we look at the summary column, how many calves had analytes out of range. And we see three calves had low lymphocytes. One of those calves had rotavirus and died. Another calf with low lymphocytes had rotavirus and survived.

So there is no predicative value there.

Two calves had platelets out of range. What does that mean? The high one died from diarrhea and the low one survived all the way to weaning.

(Slide)

So to summarize the neonatal data, that is a real brief overview. There is a lot more to discuss, but I don't think this is the time and place to get into the nitty gritty of each individual animal analyte, although we do do that.

But to summarize what we found in the neonates, there were ten clones. Two of which died. There was 92 percent similarity for the clinical chemistries and 90 percent for the hematology.

We did see liver enzymes that were different. And just to give you a peek of the next node, those liver enzymes do normalize by the next node. These animals do show the appropriate growth responses, both in their growth analytes. I don't like to use, that word factor is wrong. It should be analyte. And that was a typo that I didn't get a chance to correct.

But the growth analytes and the immune analytes do show the expected response for animals of that age. And as far as predictability is concerned, showing you which animals had analytes out of range, that didn't give a whole lot of

predictive value. Remember that these laboratory data still must be taken in the context of the whole animal.

(Slide)

Now this table is huge. We have 46 clones and 46 comparators. This is the next node. The one to six month old group. And understand that a one month old calf and a six month old calf, even though we have grouped them together, are still -- oh, boy. They still aren't identical.

So if we look at this chart, we can see, I will tell you what, I am just going to walk -- I am not going to point to the chart. It's in your notes. But I will just describe.

The calcium, phosphorous and alk phos, growth related, still elevated. Those tended to be the calves in the younger end of the group. We do see creatinine out of range. I want to talk about it because people say why do you ignore it. Well, it's low. What is the relevance of a low creatinine? I don't know. I am not sure anyone knows in this context what that would mean.

There are some low total proteins. Some are high and some are low. And we see total protein on this chart, which is done in a chemistry machine, the next chart is done by a refractometer and different calves have values out of range. Once again indicating the limitations of what your

lab can do. Lab work isn't gospel. It's subject to interpretation.

I do want to point out that -- well, those are the big findings for the chemistry.

(Slide)

The hematology, it's interesting to note that none of these animals like previously had a problem with their red cells or their white cells. There is no anemia. No leucopenia or low white counts.

We do see on this slide that the mean cell hemoglobin concentration, MCHC, four have of the 44 measured are elevated. Four red cell distribution widths. I am sorry, three of 44, RDW's are elevated.

Now these analytes indicate spread cell maturation, unusually used to describe an anemic animal. What would cause the anemia? What do you do with these values with an animal that is not anemic?

There are four of 44 in elevated basophiles. Basophiles are associated with histamine and allergy. And what do you with just this alone, with no clinical signs? It's hard to say what to do with these stand alone numbers.

Mean platelet volume. Nine out of 41 are elevated. Mean platelet volume is machine measured and it can be artificially elevated by clumping. I don't know that, but

side evidence from the slide that the pathologist said that the morphology was good and the numbers were adequate and the morphology was normal.

I do want to show that one calf, calf 100, right there (indicating.) See calf 100? Two out of 16 analytes are -- this is the only one that had a real high white count. Like 26,000, I think, is what it was. This calf had a raging umbilical abscess. Here is a calf with a disease responding normally.

Remember in this group we don't see a whole lot of diseases. So we take what we can get.

(Slide)

To summarize this group, 46 clones have blood work. There was 96 percent agreement. Three in this age group, some of which remember we got a second group of calves with no blood work. Of all the calves in this age group only three of them were reported to have died.

96 percent similarity. Expected elevation growth analytes. And glucose compared to the comparators. I do want to mention four animals from the same cell line, one died of large offspring syndrome. This is not in the blood data. This is in the health data. But it's instructive.

One died of LOS. One at about five months of age weighed 282 pounds. One same age, 197. There is 90 pounds

difference. And another one the same age at 215, 20 pounds more. So we have one cell line with four, one different outcome and three different phenotypes. And that is helpful to understand what we can expect from this technology. And I already talked about the cryptorchid calves.

(Slide)

This is a discussion of the seven clones that were present, we had data on from both the neonatal node to the one to six month old node. I have already discussed some of this. Just remember that there was liver values. We discussed whether that was low liver values have no known real cause. And then the colostrum deprivation.

(Slide)

We have one calf that had low lymphocytes and platelets. And that calf normalized by one to six months. Calf number 79 had a number of analytes out of range. And without going into great detail, we see that the analytes analyzed at the neonatal stage actually corrected by the juvenile stage, but had other problems at the juvenile stage. It was eventually culled. This calf did have some problems.

(Slide)

When we look at the one to six month old group of those seven clones, we see some interesting things. Four of them had real elevated glucose. These were not within ten

percent. We could not explain it that way. We had to look into why.

When we looked at the urinalysis, we saw that there was no glucose in the urine indicating no sustained elevation of glucose. We attribute this probably to stress. If you have ever tried to pull blood from a cow, they just don't just stand there and hold their arm out. So you do sometimes see spikes in glucose in relation to distress.

Again, the alk phos and phosphorus. These animals were on the younger end of the range, which were growing more.

The increased A/G ratio indicates low globulin. Again, these were like six week old animals with internal antibodies dropping and diogenes hadn't started up yet. Some with decreased --- gap. And we don't know what that means.

So these out of range values for this seven calf subcohort do not indicate consistent trends other than what you would expect normal physiological changes.

(Slide)

In summary, one out of range neonatal values improved by the one to six months, the out of range values just described for the one to six month old group. In context, when you look at the context, we are not clinically of concern. And one of these animals was cloned, or was not

cloned, but culled later.

(Slide)

This is a discussion of the last group of data. The oldest one, six to 18 months of age. There were 18 clones in this group and 21 comparators. There is 99 percent agreement between the clones and comparators. Again, we --- more would be, disagreement would be expected on chance alone.

I do want to mention three analytes that are actually within range, but they have gray boxes. And I don't want to give them short shrift because Dr. Rudenko discussed IGF-I and estrogen prior. We ran these analytes and we do need to discuss them briefly.

If you look at the bottom last two rows, IGF-I has none that are out of range but we have five gray boxes for IGF-I. I am sorry, that is four for IGF-I and five for estradiol. IGF-I, it's slightly increased. It's within ten percent of variation and one thing to keep in mind is to speculate that these are animals of superior genetic merit. These animals are designed to grow better. That may be involved.

The other thing to consider is IGF-I fluctuates. Its hormones are released in a pulse. And you can have issues like that influencing. But the value is very close.

With estrogen, the value is higher than the comparators but not higher than say in the reference labs. Now, we already discussed that we want to use age match comparators.

But the next step back from that is what other things can you compare them to. And these estrogen levels are within that range. And estrogen itself also has variability. It's pulsatile release. Its relationship to the onset of puberty in these animals. We don't have that information to determine if that is involved.

The other one I just want to mention, because there are a lot of gray boxes is creatinine. And creatinine, there are seven gray boxes there. They were all like, instead of 2.0, it would be 2.1. So close as to be irrelevant clinically.

(Slide)

And the hematology, again we see 99 percent agreement. And we don't see a whole lot of problems here. We see two calves with, two clones with low MCV. And we see one calf, 108 here, MCV is mean cell volume. In the context of no anemia it is hard to draw a lot of conclusions about what that means on its own.

In calf 108 you see two out of 17 problems on this slide. On the previous slide we saw five that are analytes

out of range. And this calf ended up being described as having been a dwarf and having frequent bloat and was ultimately culled.

(Slide)

So to summarize this set, 18 clones, none of the animals after six months died. We have 99 percent similarity and the IGF-I and growth hormone were only slightly elevated but within published physiologic, published ranges and physiological ranges.

As far as response to disease and predictability, well there was no real disease and nothing to predict.

That is the summary of the data set from Cyagra for bovine. Now I do have pigs and goats to talk about. And I will go through those next.

(Slide)

In 2003, Archer set out to determine what kind of variation is there within a population comparing clones to conventionally bred pigs. These animals were genetically the same age, breed. They were sex matched. In fact, they were half sibs. They were very closely related.

(Slide)

The first thing that this paper, the researcher did was look at their behavioral traits. They measured their food preferences, their temperament, and time budgets, which

a time budget is defined as the amount time spent engaged in a particular activity in their parents.

They determined, the conclusion was that the behavior was no more homogeneous than between siblings. There was a lot of variation. And they behaved as conventional animals. That is to say that there was no behavioral abnormalities.

(Slide)

They then went on to discuss physical traits to determine when comparing clones and controls. For body weights they found no differences. That 27 week old clones and control animals were about the same age and within the range for that breed.

As far as phenotypic variation, the teat pattern would be six on one side and six on the other for most. One had six on one side and seven on the other. And that is also within the range in a normal pig.

For skin, there was hair growth pattern. One had a unique hair growth pattern with coarse hair. And I will show you a picture of that. And one had hyperkeratosis, or thickened skin as seen on histology. The paper doesn't mention if those were the same pig.

(Slide)

But if you look at this picture, you can see this

pig with coarse hair and this pig with smooth hair. And those animals are from the same genetic line.

(Slide)

So that is an example of the phenotypic variation seen with animals with the same genotypes. So we see also that large and small clones are side by side. Again, same donor cell. And the smaller clone in the next picture I am going to show you never reached the weight of the size of the other clones.

(Slide)

And these two clones are from the same donor and they were farrowed, that is born, by the same dam. You can see these. Again an example of identical genotypes displaying different phenotypes. I discussed this, the Cyagra data, with those four cows, one of which died of LOS and the three others with different phenotypes.

(Slide)

We also had blood work which we reviewed they submitted. And this was nice because this confirmed what we saw in the cattle, which is if you look at Alk phos, not calcium for some reason, but phosphorous, those two analytes were elevated in the young animals that were rapidly growing and dropped off at appropriate levels as they got older.

And we see the same thing with globulins. This is

a measure of immune function that young animals have lower globulin and they get higher as they get older. Same with the clones as the controls.

(Slide)

So in summary, in pigs, the clones and the comparators are relatively indistinguishable. Via either lab values or with behavioral studies. We see appropriate response in growth analytes and appropriate response in the immune status, globulins and such.

We don't have the data on sheep. So I will skip those and go to the next species, which is goats.

(Slide)

In a study, 27 transgenic and 70 non-transgenic goats, embryos rather, were implanted into 13 recipients, an average of seven embryos per dam.

Of those five were confirmed pregnant at day 35. Of those five, four of the recipients delivered five male kids and one recipient delivered one female kid.

(Slide)

The birth weights in cotyledon numbers were not significantly different from naturally bred goats at the same facility. Of the six goats that were derived from this process, three of them died. One at 24 hours, one at one month and one at three months. And those all died of

respiratory infections.

(Slide)

In another study we see 91 embryos implanted into eight recipients. Four were pregnant at day 30 and delivered 7 female kids of which one died at birth. 54 male embryos were implanted into six recipients. One was confirmed pregnant and that confirmed pregnancy maintained and delivered two male kids. One died at birth.

The point of this slide that all of the goats maintained pregnancy to term, which is something that goats seem to be particularly good at. Again, it's species difference that goats have.

(Slide)

The average birth weights were similar. And the average cotyledon number was similar.

(Slide)

Half of the goats had poor suckling reflex and they were fed by orogastric tube and that responded by day two, or resolved rather by day two. These clones were described to appear healthy. The routine blood profiles were monitored and described to be normal by one year of age, although no data were submitted on that, I don't think.

And they described that these kids were within normal ranges for normal growing Nigerian Dwarf kids.

(Slide)

In summary clones that survived the first few critical days of birth are mostly normal and healthy.

(Slide)

The anomalies aren't qualitatively different from other assisted reproductive technologies but there is an increased frequency. In the perinatal node we see mortality, placentation, large offspring and such. We don't see that this is necessarily common across all species.

In the juvenile node, we see less problems. Remember we talked that the hormone levels are similar and the behaviors are similar. Mortality is lower in the juvenile node.

In the reproductive and maturation nodes, there are no apparent problems, although the data are sparse. And the growth parameters and the fertility between clones and comparators are very similar.

Next I would like to introduce to you Dr. Amey Adams. She will discuss what the data we have discussed tells us, what we can conclude on animal safety.

Conclusions for Animal Safety

by Dr. Amey Adams

DR. ADAMS: Good morning. My name is Amey Adams. I am an animal scientist and I work with Dr. Dubbin in the Ruminant Drugs Team at the Center for Veterinary Medicine. And I will be talking to you today as he indicated on the risk conclusions that we drew on animal health based on the data that we had available.

(Slide)

And I will just remind you of Dr. Sundlof's introductory remarks. The question that we started out with was whether or not the risks experienced by animals involved in the cloning process differ qualitatively from those experienced by animals undergoing other assisted reproductive technologies.

We have all heard reports of increased incidents of health problems in young clones and their surrogate dams compared to natural breeding. But how did that compare with other artificial, I am sorry, assisted reproductive technologies such as artificial insemination and in vitro fertilization. Were they different in kind or were they different in frequency?

(Slide)

Both Dr. Dubbin and Dr. Rudenko walked you through

this slide. I won't spend a whole lot of time on it for that reason. But just to show you that we had slightly different interests when we looked at animal health, specifically.

In the cell fusion through fetal development phase, as Dr. Rudenko and Dr. Dubbin mentioned, this really sets the stage for the perinatal period and the subsequent development of the young clone.

It also is, particularly in mid to late gestation, a time when we were concerned with questions regarding the development of hydrops, which is a late pregnancy condition that occurs in cattle and sheep. Whether or not if in fact the fetus is not viable, whether the cow or sheep is able to expel that fetus normal and return to cycling and normal reproductive activity.

Then in the perinatal period we were interested in, we had concerns about large offspring syndrome, as well as hydrops and dystocia. So we looked at birth weight, the dam's readiness for delivery, the onset of lactation, and mothering behavior, and newborn organ function and IGF-II levels in the newborn clones.

And for the juvenile clones and for the later stages we were mainly interested in the continuing development of the animal, of the animal clone. How well it matured. Whether it came into puberty normally. And it's

continued health following those early stages.

And we also looked for information on the progeny of clones. And I will just point out that as we progressed past the perinatal period, the data became more and more sparse.

(Slide)

So just in general, these are the life stages and the animals that we are looking at for the assessment of animal safety. And we will begin with surrogate dams.

(Slide)

And as we sorted through the literature it became apparent that different species experience different outcomes. As Dr. Dubbin pointed out, we have a large data set on bovine clones.

Very little quantitative, if any quantitative, information on sheep. But the qualitative reports that we have on sheep are consistent with what we see in cattle and so we have grouped those two species together. Whereas, goats and swine seem to experience much fewer problems.

And the studies that we reviewed indicated that there is an increased risk of mid to late gestational complications such as hydrops, which is a condition that involves edema of either the fetus or the fetal membranes. Dystocia, which is difficult labor or difficulty giving

birth. And a few other reports of very few observations of other types of complications, which I will discuss in a moment.

(Slide)

Hydrops, for those of you who are not familiar with the term, it's a collective term referring to the excess build up of fluids in the fetus or the fetal membranes. It is a rare condition in naturally bred and conventionally bred cattle. It occurs at about one in 7,500 pregnancies in the general population of cattle.

It is more common in in vitro fertilization, occurring at a rate of about one in 200 pregnancies or one-half of one percent of in vitro fertilized pregnancies in cattle.

Now because this condition is so rare in the general population of cattle we realized that the majority of large animal veterinarians will not have had experience in dealing with a hydrops pregnancy. And for this reason we decided to contact some of the clone producers to discuss with their veterinary staff their experiences with hydrops, both in terms of its frequency of incidences and the pathology of the condition.

And one of the things that they indicated was that this condition can be detected as early as the sixth month of

pregnancy in cattle. Cattle undergo a nine month pregnancy. So it would start to show up usually late in the second trimester and from there on.

(Slide)

Another thing they indicated to us was that the degree of severity of hydrops varies from mild to severe. Some cows will experience mild hydrops. It does not pose a risk for either the fetus or the cow. She goes through the pregnancy normally and is able to deliver a viable calf.

On the other hand, there are cases of severe hydrops. They have been reported in the literature. And if it does in fact progress, becomes worse, and the pregnancy is not terminated, it often results in the death of both the fetus and the dam.

The incidence we found as we reviewed the literature and as we talked to cloning companies, the incidences are highly variable among laboratories. And can range anywhere from as low as one-half of one percent to as high as 15 to 17 percent, depending on what study you are looking at, what laboratory you are looking at.

The data do indicate and the clone producers agreed that the risk of hydrops is higher in clone pregnancies compared to in vitro fertilization pregnancies.

And I just point out here that the Pace, et al,

study, some of those cows were carrying transgenic clones. But in pregnancies that survived beyond 60 days, and there were 178 of those, 30 of those cows developed hydrops.

Other clone producers that we spoke with indicated that the incidence was as low as one in 200 or one in 300 pregnancies. So considerable variability there.

(Slide)

And dystocia is a problem that occurs in all species of mammals. And it's just difficulty delivering the calf or delivering the fetus. It's most often caused by fetal oversize compared to the dam's pelvic opening. It can also be caused by malpresentation, such as a breach birth. Or in the case of twins or other multiples, when you have simultaneous presentation.

In conventionally bred cattle, both dairy and beef, the incidence is about four to six percent. And in sheep it's quite a bit higher. It's actually ten to 30 percent depending on the breed.

(Slide)

In clone pregnancies dystocia is often the result of fetal oversize. As we mentioned before large offspring syndrome, which I will get into when I discuss the neonate. It is a problem for the dam, because it can result, depending on its severity, it can result in retained placenta, uterine

infections. Can cause permanent damage to the reproductive tract. It can even cause musculo-skeletal damage.

And in those last to instances, this could compromise the animal's ability to return to the herd to reproduce. She may be culled due to reproductive failure or other injuries.

And incidence of dystocia in clone pregnancies, as I mentioned, is associated with the large offspring syndrome because these calves are not able, are so large they can't pass easily through the pelvic opening.

(Slide)

Some less frequently noted complications, and we don't have really any numbers to go along with this, are poor or absent mammary development. Absence or atypical signs of labor, also known as uterine inertia. Agalactia or failure to lactate. And impaired maternal behavior.

These are more of a complication for, or a problem for the neonatal clone than they are necessarily a risk to the dam. Although they are happening to her, it has greater implications for the newborn.

If the cow fails to lactate that has implications for the calf's ability to obtain colostrum, which is the source of passive immunity, it obtains from it's mother. It also has implications for the calf's early nutrition.

And it is also very important for the dam to interact appropriately with the newborn calf or lamb by licking it, stimulating it to breathe, to stand, to suckle and to form that maternal bond.

(Slide)

It is interesting that in goats and swine we have no reports of complications in surrogate goats. And no reports about a hydrops or a large offspring syndrome in either goats or swine surrogate females.

There have been some reports, based on our discussions with clone producers and one study on clone transgenic swine, of lack of mammary development, failure to lactate, and uterine inertia. And as I mentioned those last complications are more of a problem for the neonatal clones than they are necessarily a risk to the dam herself.

(Slide)

Let's talk about large offspring syndrome for a minute. Dr. Dubbin touched on this. It was reported, it has been reported in in vitro fertilization, blastomere nuclear transfer, which is early embryonic clones, as well as somatic cell nuclear transfer clones of cattle and sheep.

It's typically characterized as the fetus or newborn, which has a body weight greater than 20 percent above the average weight for its breed and sex. It's often

accompanied by respiratory complications.

Sometimes the lungs are immature. They fail to inflate. Or, in case of dystocia, the calf may wind up inhaling amniotic fluid, which sets the stage for pneumonia later on.

There have been some internal organ defects reported, particularly the heart and kidneys. Musculo-skeletal defects, including tendon retraction and some joint and skull malformations. And the calves are often slow to stand. And have a poor or absent suckle reflex.

(Slide)

Large offspring syndrome increases the risk of dystocia. As I mentioned, a large calf is going to have a hard time passing easily through that pelvic opening in the dam. This is a source of stress to the neonate as well as being a problem for the dam.

And it increases the risk of mortality and morbidity. Due to premature separation of the placenta the calf is deprived of oxygen. It may be forced to try and breathe and winds up aspirating or breathing in amniotic fluid, which sets it up for respiratory complications later on.

(Slide)

Some of the complicates related to LOS are

reversible depending on their severity. Tendon, flexor tendon contracture, which is commonly noted in these calves often resolves on its own or in response to therapy. Also respiratory conditions are often amenable to treatment with supplemental oxygen.

The incidence of LOS is also variable among the labs and can range anywhere from eight to 50 percent depending on what study you are looking at. And just to compare that to large offspring syndrome in in vitro fertilized calves, they also have quite a wide range.

Anywhere from seven percent in an early study by Hasler, et al. And up to 31 percent in the Kruip and den Daas study, which was a survey of several European countries and a variety of assisted reproductive technologies.

(Slide)

Based on the information that Cyagra provided us, the critical survival period appears to be the first 48 hours after birth. Now the neonatal death rate, and it's interesting whether we are looking at transgenic clones or non-transgenic clones, the neonatal death rate in cattle appears to be around 20 percent during that first 48 hour period.

In the IVF studies that were conducted in the mid-90's, the range was 14 to 16 percent during this same

period of time.

(Slide)

Now we have far fewer data to look at in goats and swine. We have two reports that were published which indicated mortality in neonatal goat clones. They were both conducted by Dr. Keefer.

One kid that succumbed to a respiratory infection at one day of age. And two kids that died during the process of labor. These were both twins. Two surviving clones. We don't have any more information on those animals.

There are few reports of complications in neonatal swine. Both Polejaeva and Walker, et al., reported low birth weights, but it was just a mention in passing. The actual frequency of these low birth rates was not reported.

And we only have one report of physical deformity in a non-transgenic cloned pig that was one out of 28 pigs, which was born with anal atresia, which is the absence of an anus.

Now these problems have been noted in conventionally bred goats and swine as well. But again because the numbers are so few, we really don't have a way of comparing to decide whether there is any difference between the incidence in clones versus the incidence in conventionally bred animals of these species.

(Slide)

Let's move on to the juvenile period. And just generally speaking across species for juvenile clones, most reports indicate normal growth and development following the neonatal period.

The behavioral studies that have been conducted in cattle and swine note no abnormalities. And results of blood tests, I mean we actually had several papers on that as well as the Cyagra data set, indicate that cattle and swine in this age group are mostly within the range of their conventionally bred comparators, animals of the same age.

(Slide)

For cattle, this is mainly from the Cyagra data set where we actually had some individual animal data, a few animals were reported to have health problems. And most of these seemed to relate to congenital problems that were observed at birth related to large offspring syndrome.

There were two animals that had flexor tendon contracture that did not respond to therapy. A calf diagnosed with failure to ---. GI tract problems. Heart abnormalities.

But what really stood out to us was the large number of umbilical surgeries that were conducted in this period due to enlarged umbilical hernias and the like. There

were 29 of those out of 134 animals.

(Slide)

Again, the data in goats and swine is rather sparse. We have one report of two goats that died of respiratory infections during the juvenile period. And one report, as Eric discussed, of hyperkeratosis in a swine clone.

Both of these may be related to management. We know that respiratory infections are a problem in goats. Hyperkeratosis most often is related to a nutritional imbalance.

(Slide)

There are some other complications which may be associated with the genetics of the donor. Eric, Dr. Dubbin, discussed these in brief. Cryptorchidism, all of the calves from the same bull, from the same cell line. And dwarfism. Both of these are problems that are related to a recessive gene in cattle.

Hyperkeratosis in swine, I mention this same pig, because we really don't know very much about the diagnosis and when it took place or anything about the nuclear donors. But there is genetic recessive gene that causes what is called dermatitis vegetans, which is a type of hyperkeratosis in swine.

(Slide)

So for the puberty and reproductive maturity period, again, for pubertal cattle, we didn't have any data at all on sheep, not even qualitative data for sheep. So I will just talk about cattle for this period.

No health problems were noted. The data from Cyagra indicate that blood chemistries in animals in this age group are normal. Most reports indicate that heifers reach puberty, conceive and deliver healthy calves. Again these are just cursory statements. Not a lot of information there.

There was one study by Enright, et al., based on four cloned heifers which indicated that these particular heifers reached puberty at a slightly later age than their age match controls. But they were within the normal range for their breed.

We don't have any detailed information on bulls. There have been a couple, again, cursory mentions that bulls were noted to produce semen and produce offspring. That is about all we have on that.

(Slide)

For other species, we have one report each on fertility of rams and buck clones, male sheep and male goats, indicating that they were normal at the age of puberty. And the Gauthier study in particular of goats looked at fertility

and sperm quality measurements and found those to be the same as their age matched comparators.

And we have one report of a goat doe clone that conceived and delivered normal offspring. No reports so far on reproduction in swine clones.

(Slide)

On maturity and aging, this is where we start running out of information on livestock. Basically because not enough time has passed to be able to evaluate this in these animals. We have several studies on aging in mice that we looked at. One noted shorter life spans and increased health problems in older mouse clones.

We also looked at studies of telomeres. And telomeres are sections of DNA which are thought to be an indicator of aging because they shorten as the animal grows older. Well we found that these studies were often conflicting. Dolly was reported to have the same length of telomeres as her six year old nuclear donor.

Studies in cattle have indicated that the cattle have telomeres that are the same length or longer than their age matched comparators. And one study by Kubota, et al., indicated that it depends on which tissue you look at what the length of the telomere is. So we felt that it probably was not a very good predictor of lifespan.

(Slide)

For offspring of clones, again we are very sparse on data. Mostly just cursory reports that state, yes, they had offspring. They are normal and healthy. No details available in farm animal species.

So, again, we looked at reports for mice. And we have two of them that indicate that there were some abnormal clones that they bred. In the case of Shimazowa, et al., they took clones that were born with their eyes open that were abnormally large and had abnormally large placentas. They bred them. They had normal offspring. The offspring were born of a normal weight. They had normal placentas. And their eyes were closed as they should be.

And the Tamashiro, et al., paper looked, again this was the obese phenotype that Dr. Rudenko mentioned. That the clones developed. They did not pass this phenotype onto their offspring.

(Slide)

So just to conclude, and again, I have broken these out into the species because of the differences that we see across species. The critical period appears to be late gestation through the first post-natal days for both the surrogate dams and the clones. This is the time period with the highest incidence of health problems and of mortality.

The risk of perinatal morbidity and mortality are higher in clone pregnancies compared to other assisted reproductive technologies. Most clones that survive this period appear to be healthy and similar to conventionally bred counterparts. And so far no abnormalities have been reported in the offspring.

(Slide)

For swine, we have a few reports of complications in surrogate sows. They do not seem to be a risk to the dam. We don't believe them to be a risk to the dam. Although they might be a problem for the neonates.

We have one report of deformity in a clone pig, anal atresia. It has also been noted in conventionally bred swine. And so far no reports on reproductive maturity of clones or the health of their offspring.

(Slide)

For goats, no complications noted for surrogate does carrying goat clones. Very few health problems noted in the goat clones themselves. Two deaths during labor. And three deaths due to respiratory infection. They appear to have matured normally and produced healthy offspring.

(Slide)

So overall we would have to say that all the complications that we have seen have been reported in studies

of other assisted reproductive technologies, particularly in vitro fertilization. The frequency of the anomalies is increased relative even to in vitro fertilization.

The adverse outcomes that we have observed are more frequent in cattle and sheep compared to swine and goats.

(Slide)

So just to remind you of the question that we posed to our advisory committees is based on what we have presented, has the risk assessment that we have done adequately identify the hazards and characterized the risks relating to animal health.

And with that, I will turn it over to Dr. Rudenko to discuss food safety consideration.

Conclusions for Food Safety

by Dr. Larisa Rudenko

DR. RUDENKO: Well it stands to reason that the talk on food consumption comes right before lunch.

(Laughter.)

(Slide)

DR. RUDENKO: I want to remind the Veterinary Medicine Advisory Committee that we do have a question to pose to you, just as Dr. Adams posed to you. So the cloning risk assessment asked the following question. Are the edible products derived from animal clones and their progeny as safe to eat as the edible products derived from their conventional counterparts?

And what we are asking you, in particular, is based on what we have presented, has the risk assessment adequately identified the hazards as we have defined them and characterized the risks, again as we have defined them, related to food consumption?

(Slide)

I just need to remind you one more time what the criteria and assumptions are that we are using in this evaluation. And then given that we are running quite over time, I will go through these rather quickly and get straight

on into our preliminary conclusions.

(Slide)

Remember we dealt with a two-pronged approach. Two prongs are interdependent but address food safety from two different perspectives. One asks the question whether or not one assumes that healthy animals are likely to produce safe food. And the other one asks questions about the comparability of the composition of the food relative to corresponding products from conventional animals.

Remember that unlike the animal health assessment, the critical biological systems approach for food safety is looking for subtle hazards. We are not looking to see whether an animal is frankly deformed because our assumption is that just as conventional animals, those animals will not enter the food supply. So, we are looking for subtle hazards in these animals.

The compositional approach, of course, considers the available data.

(Slide)

Again, I want to remind you that this is a qualitative comparative risk assessment. We are not looking for a specific numerical value associated with risk. I will remind you that the certainty of safety is always approached but never reached. Our goal is to get as close to certainty

as possible, always to be protective of the public health.

And that the strongest statement that we can issue in this risk assessment, because it is a qualitative comparative risk assessment, is that something is as likely to be as safe as, where our comparator is conventional food animals.

And, again, so what does that mean? We are looking to see if the food from animal clones is as safe to eat as the food that we eat everyday from conventional animals.

(Slide)

We will present the conclusions just as we presented the methodologies, species by species, except for bovines where we have the largest data set where we will talk about a couple of life stages.

We will present to you a weight of evidence evaluation, summarize the empirical observation. Make a comment about consistency with other species. Try to identify what uncertainties we can. And give you some indication of the level of confidence we have in those conclusions.

(Slide)

Okay. Remember that our underlying biological assumptions are that food animals do not produce toxins. There are no introduced genes from other sources. As I

previously said, obviously malformed or diseased animals are culled, do not make it into the food supply.

We are looking for subtle hazards. We have agreed that perinatal clones may be quite fragile. And the other biological assumption that we have that is backed up with data from a model system is the gametogenesis. The process of creating sperm in egg in sexually reproducing animals may clear the genome of inappropriate signals, reprogramming signals that may result from somatic cell nuclear transfer.

(Slide)

So when we looked at the first developmental node, which was a cell fusion and fetal development, we came to the same conclusion that Dr. Adams came to for animal clones, which is that this stage sets the stage for further development. But by itself it's difficult to extrapolate from results that we may have observed here to food consumption risks.

We know that the probability of implanted embryos developing to viability is quite low. But it appears to be improving as the technology becomes more common place.

The animals are at high risk, developing animals are at high risk, as can be their surrogate dams depending on the species.

We know that the lack of success here is likely due

to two factors. One may be technology. It may damage the oblast or the donor as you are doing the injection or the fusion. And there are also biological reasons for this, such as the incorrect reprogramming of the donor genome.

(Slide)

Now we go on to a species specific analysis. And let's start with perinatal bovine clones. We will ascend in age to adults. Our preliminary draft conclusions stated in the draft executive summary are that perinatal clones may pose a limited risk for consumption as food.

The empirical data on which we based this conclusion is the consistently reported relatively poor condition of these animals at birth and the relative instability of their physiological parameters.

That doesn't mean we think they truly are a risk. But we cannot, based on the data that we have available at this point, say that those animals are indistinguishable from their comparators. And, therefore, they may pose some small risks.

I want to make the comment right now that will be constant through the rest of this analysis, and that is that we at FDA do not assume that any clones will be primarily directed to the food supply. These are expensive animals. They are difficult to produce. And therefore they become

extremely precious to both the producers and the breeders.

So it is unlikely that these animals will actually enter the food supply. What is much more likely is that these animals will be used as breeders and the progeny will enter the food supply.

So even though we go through the systematic analysis of clones themselves, we want you to understand again that the probability of these animals entering the foods supply is relatively low.

(Slide)

Now to go on to juvenile bovine clones. For this case we believe that edible products from juvenile bovine clones are likely to be as safe to eat as those from non-clone juvenile cattle. We base this on the survey of the data that Cyagra presented to us. And the consistency with the peer reviewed literature.

Juvenile clones tend to be largely health and normal. They exhibit appropriate physiological responses to developmental signals. And the early physiological instabilities that we have seen in the perinatal animals tend to resolve over and within this time period.

We were not able to detect any food consumption hazards in the biochemical parameters that we investigated here. Either in the Cyagra data set, the studies from

Chavatte-Palmer, in which you saw levels of IGF-I, IGF-II, thyroxin, and so forth, all resolved by the latest 50 days of age.

In the Archer studies of the pigs, in which all of the animals showed age appropriate developmental signals, and no biochemical parameters out of range with their passive related comparator animals.

(Slide)

So we have consistency here with the biological assumption that clones will use the juvenile period to resolve any instabilities that occur physiologically. Consistency with other domestic livestock species. That is cattle and pigs. And consistency with the mouse model as well.

We have relatively few uncertainties about this time period. The data set is relatively large. Due in large part because of the rather large data set we have in the literature on cattle and this time period as well as the Cyagra data set. And it is entirely consistent.

So therefore our confidence in this estimate is relatively high. And the comment that we would like to make again here is that these animals are unlikely to be primary producers of food.

(Slide)

Finally getting to adult bovine clones. Our preliminary conclusion here is that edible products from adult bovine clones are likely to be as safe to eat as those from non-clone adult cattle. Again, the empirical basis on which this conclusion arises stems in large part from the animals from the Cyagra survey where healthy adult clones were virtually indistinguishable from the comparators.

All of the earlier physiological instabilities in the populations of animals have been resolved by this time. The literature results are entirely consistent with this, even those studies in which physiological parameters have been taken and cattle show complete resolution of any instability by 50 days of age. And there are quite a number of studies that take a look at this.

The information that we have on reproductive function is, as previously stated, perfunctory. But it does indicate normal functionality.

So here again we have consistency with the underlying biological assumption that as clones age, they become more physiologically stable and function indeed as copies of their donor animals. There is consistency with other domestic livestock species and the mouse model.

We have relatively few uncertainties here. Although additional reproductive data could confirm the

cursory reports and we would again, as we have done from the podium in many other times, asked producers of clones who have such data to make it available to us.

(Slide)

Our confidence in these conclusions is quite high for the reasons that we have discussed. Again, I remind you that these clones are unlikely to enter the food supply as meat for economic reasons. But milk from adult clones may enter the foods supply from lactating breeders.

(Slide)

So remember I talked to you about bounding the risk space and trying to be very systematic about identifying where our biases might be and where we started out and where we ended up. This is our internal self-check on ourselves.

We started out from the hypothesis two, which as you remember, was the bound that said animal clones may appear to be copies, but you really need comprehensive data to prove that.

And so what we did was we went through a rather comprehensive database. And based on those data, we decided that the weight of evidence moved us from hypothesis one to hypothesis two.

(Slide)

Swine. Our preliminary conclusions regarding the

safety of consumption of food products from swine clones is that edible products from those animals are likely to be as safe to eat as corresponding products from non-clone swine.

Now the data set here is a bit more limited than it is for bovines. And I know that some of the clone producers who have clone swine have submitted some data to us and we have not had a chance to evaluate that. These conclusions are drawn independently of those submitted, but non-evaluated data.

The swine cloning appears to be technologically a little more difficult than cloning cattle. But piglets generally appear to be healthy when they are born. The Archer studies from the Laboratory of Jorge Piedrahita indicate that the behavior appears to be age appropriate and entirely normal. As do the health and the physiological measures, which appear entirely normal within the range of closely related sibs and reflective of normal developmental function.

So we feel pretty confident in saying at least for the animals that we have been able to look at, they are not materially different from comparators.

Here we have consistency with biological assumptions, other livestock species. And I am sorry there is a missing mouse model here too. It is entirely consistent

with the mouse data. This data set, because it's smaller, causes a few more uncertainties for us. It would be nice to have additional data on reproductive function of these animals, because we really have none.

And the confidence in our conclusions is tempered by the size of the data set. It would be nice to have as much data as we had for the cattle. But the data that we do have is entirely consistent.

The Archer studies are indeed compelling. And they increase our confidence in the estimate. But still we do not have the same level of confidence as we did in the cattle. And again I remind you that clones are not likely to be used as meat and we don't get a lot of milk from pigs.

(Slide)

So we started out with an initial hypothesis of two. Again, you know, we needed more data. We needed a fair amount of data to show that these animals didn't just appear to be copies. And the weight of evidence moved us to about a hypothesis one minus. We are pretty comfortable saying that there are good copies, but we would really like to have a little bit more data for pigs.

(Slide)

We have nothing at all on sheep. So we will move right to goats.

(Slide)

Our preliminary conclusions on the safety of food products from goat clones is that they are likely to be as safe to eat as corresponding products from non-clone goats.

Again, the empirical basis for this decision is from a small but entirely consistent data set. Goats appear to be extremely cloning friendly. Their behavior appears to be age appropriate and normal.

Health and physiological measures appear normal and reflective of normal developmental function. There is one small, but detailed, study of normal reproductive function. And remember we said we put a lot of weight on good reproductive function as an integrative assessment of the health of the animal.

(Slide)

So here we have again consistency with underlying biological assumptions. Consistency with observations in other livestock species. And, again, the mouse model got left off this slide.

And we have some uncertainties with this data set. And I think they are a little more, our uncertainties are higher than they are for cattle, but different from the uncertainties that we have for swine.

We believe that we would have more certainty in our

conclusions if the --. One of the things that Dr. Dubbin didn't tell you about, in large part because of the shortness of time, and because the data are preliminary, is that there is one abstract out there in which there are some physiological data similar to the ones that you have seen for cattle and pigs. It's extremely cursory. It's in abstract form. It hasn't been published as a peer reviewed publication. That is tantalizing but not probative.

So we would feel much better if those data were indeed published or made available to us. Unfortunately it's a business decision not to publish those data at this point. And so our confidence would be increased if those data were indeed released to us.

And, again, we just want to comment that goat clones are not likely to be as major producers of milk, although it is entirely possible, but milk from lactating breeders would enter the food supply.

(Slide)

We have gone here from hypothesis two to hypothesis one. We have relative -- and this is a little bit higher than our swine, because of the very high weight that we placed on the reproductive function as indicating normative integrative function of the animal.

We based that on biological consistency that we see

among species. A small but high reconfirmatory data set.
And the weight that we placed on the reproductive function.

(Slide)

Now progeny. These are the animals that are likely actually going to become meat and from whom we will likely obtain milk, should these animals enter the food supply.

Our preliminary conclusion here is that edible products from the progeny of healthy clones are likely to be as safe to eat as those from conventional animals.

Now you notice I didn't say as progeny from conventional animals, because all conventional animal are progeny. We don't start talking about the initial animal and then descend down.

The biological assumption on which we relied quite heavily is that gametogenesis naturally resets abnormal epigenetic signals should they occur in the clones themselves. And much of our confidence here comes from the mouse data, which is more extensive than any of the information that we have in livestock, which as we have said over and over, tends to be cursory.

(Slide)

Again, the data from livestock is cursory. There are very short mentions in papers. Such and such an animal was bred, progeny or normal. Or you will hear in

conversation we have bred this bull, we have bred this heifer and the calves are great. But we don't actually have the data in hand to analyze.

We do have compelling data from the mouse model and it is compelling. We have a limited report of comparability of bovine milk. Remember I told you in the Walsh study, there was one animal that was the progeny of a bull clone. And that cow gave milk that was comparable to the comparator animals.

And we have limited reports of reproductive function of progeny goats. The Gauthier study that both Dr. Dubbin and Dr. Adams mentioned, had one sexually reproduced offspring of a goat clone. It was a male. And it seemed to be entering puberty at about the right time and behaving appropriately.

(Slide)

So that is where we are based on the critical biological systems approach. The first prong of our two-pronged approach. Now let's get to the second prong.

(Slide)

The compositional analysis of bovine milk is considerably more limited than the data base that we had to work from from animal health.

There is one peer review study that I have

discussed with you. There is one abstract that we didn't discuss that had cursory mention. The peer review study is entirely consistent with the prediction that animals that are virtually indistinguishable from comparators will likely produce milk that is similar to the comparators.

One of those animals, as I said previously is the progeny of a clone. But we have a small sample size. Any differences that do occur or that might occur could be due to breed and husbandry differences. It was not a particularly tightly controlled experiment.

But, again, I remind you that studies conducted in agricultural environments are not as tightly controlled as studies that are conducted, for example, in laboratory animals. And this is, after all, a survey and not necessarily an example.

So more data would really increase our confidence and judgments regarding whether or not material differences exist between the milk of clones and their progeny and conventional animals.

(Slide)

So we started thinking about well, if we could get the comparative data that we wanted, what would we ask for and how would we look at it?

So the first question I asked, because I am not a

dairy scientist by training was what is milk. I went around the agency and asked, "What's milk?" And the Code of Federal Regulations states that

"Milk is the lacteal secretion, practically free from colostrum, obtained by the complete milking of one or more healthy cows."

This also applies to sheep and goats.

(Slide)

And then we asked well, what is meat? How do you define meat? Well the Code of Federal Regulations says it's, "The part of the muscle of any cattle, sheep, swine or goat, which is skeletal ..." And you can read the rest. And it does include lips, snouts, or ears.

So given that those are the regulatory definitions that we have, we frankly don't have any chemical formulas that define either of these commodities. And it's important to note that they are indeed commodities.

They are not specialized products that have a certain set of specs. The Pasturized Milk Ordinance tells you that you have to have a certain amount of milk fat and things like that, but it doesn't tell you anything really beyond that.

The other thing that we know is that we fortify milk with Vitamin D. So don't go looking for Vitamin D

levels in milks.

(Slide)

What else do we know about meat and milk? Well a survey of the literature and a fairly extensive survey of the literature including various USDA databases indicates that the composition of meat and milk can vary significantly, even within the same breed. Even within the same animal, depending what stage of lactation it's in. Depending on the season, the climate, the diet the animal is receiving, the age of the animal. And with respect to milk, where it is in the lactation cycle and how many cycles of lactation it has had.

So even for experimental purposes, as I tried to tell you before, it's very difficult to control the conditions under which you obtain milk from animals to do a good comparison.

So, it doesn't really look like exact compositional analysis is practicable. We just don't know how to define the comparator for a complete tightly controlled chemical analysis. So what could we do that would be practical, informative, and give us a good handle on risk?

(Slide)

Well the first thing we decided to do was to narrow down the comparators we could use to compare against. And we

asked the question, well, do you want to compare it against, do you want to compare cloned milk or cloned meat against genetically closely related animals? For example, the half sibs that were in the Archer study that you heard about.

That would tell you what the effect of cloning was on that particular breed or genetic background. But how would you account for normal epigenetic variability in the comparator population? We already know that if you give a lot of methyl equivalents to certain animals, they will have different levels of gene expression, than if you feed a diet that is low in methyl equivalent.

How would you do the statistics on this particular analysis? So okay, we answer the question on what -- that is one set of questions that we could ask. As you can tell we like to bound our questions from both sides.

The other way to look at this is to look at commodity products. What we eat and drink every day. So we could look at comparisons to bulk tank milk, which is what you get when you go to the Giant or the Safeway. Or when you go to the butcher shop.

So that would provide a more extensive comparator range for conventional counterparts. But then how do you account for the variability in the comparators? How do you know that the beef that is at your Safeway, you have two

packages of beef in your Safeway. One of which comes from an Angus from Texas and the other of which comes from a black cow of mixed parentage grown in Virginia. They are going to differ.

(Slide)

So again we come back to the issue that we discussed previously. To look at whether or not there is a food consumption risk. What are the actual hazards we are thinking about? And for us here, the question was one of nutritional risk.

Remember we are not introducing anything new into these animals. So we don't have to worry about the presence of some exogenous substance. We are looking to see is this milk or meat providing you the same dietary equivalents that you are receiving from conventional foods.

And as you may remember, we came up with a short list, not terribly short, of analytes that we believe would cover most of the dietary, major dietary requirements that are met from milk and meat.

If any clone producers are out there, we would really like to have some more data on this.

(Slide)

But what I really want to ask the Advisory Committee is a provocative question. Given the highly

detailed physiological information that we have on some of these clones, what would be the additional scientific merit in obtaining a lot of compositional information on milk, on meat?

I am not saying we shouldn't get it. But what would be the relative merits of doing that and how would it increase our level of confidence in our preliminary assessment of food safety if we had those data?

(Slide)

So having asked you that question right before lunch, you can ruminate on it while you eat.

(Laughter.)

I would like to make some concluding comments. First of all, it is important to remember that these are preliminary conclusions drawn on a complete analysis of the data that we currently have in hand, of the data that we have current analyzed, which does not include all of the data that we have in hand, which will be incorporated in the subsequent iteration of the draft risk assessment.

Our preliminary conclusions based on the data that we have evaluated so far with respect to food safety are that edible products from normal healthy clones, or their progeny, do not appear to pose increased food consumption risks relative to their comparators.

We have relatively high confidence in this conclusion based on empirical evidence from bovine clones, consistency of responses from other species.

(Slide)

With respect to progeny, our preliminary conclusions are that edible products from cloned progeny are likely to be as safe to eat as products from non-clones. Again, based largely on biological assumptions, compelling evidence from the mouse model, limited but consistent observation in domestic livestock.

We believe it would be very useful to have additional data on the health status of progeny and the composition of meat and milk. As we believe it would likely increase the certainty of our conclusions, but we wait for your advice on that as well.

Thank you all very much for staying a little late for lunch. I hope you enjoy it and come back this afternoon for our discussions.

(Applause.)

MS. SINDELAR: This concludes our morning session. Restaurants within walking distance are listed on a flier that are on the registration table outside the door. Please return at 1:30. Thank you.

(Luncheon recess was taken.)

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

1:37 P.M.

MS. SINDELAR: I hope everyone had a very pleasant lunch. This portion of the meeting is seeking clarification from VMAC and the public. Any questions regarding the talks that have been presented this morning. And I am very fortunate that Dr. Matheson has agreed to be a better moderator at this time for directing these questions to the appropriate person. So, John Matheson, please. Thank you.

Questions for Clarification from VMAC and Public***by John Matheson, Moderator***

MR. MATHESON: Maybe from the Advisory Committee, do we have questions about the presentations this morning or things about the data that we can ask the speakers while they are up here? Yes, Rich.

MR. WOOD: I appreciated the clarity of the presentations. I anticipate the comments that will come later. I was confused in looking at the data that was provided, when it described how different terms were being used, if we were comparing apples to oranges or apples to bananas. And I wasn't real sure.

It was said that the comparison note with the clones was going to be with ART's, assisted reproductive

technologies. But then I heard one study or two perhaps, the Cyagra study where it was presented as comparing the clones with comparators. And were those comparators a tease or was that data looking at the general population in those goat statistics?

DR. RUDENKO: I think, and I will let Dr. Adams finish some of this. It's important to understand that where the comparator is being placed. For the food safety, for the overall analysis of the Cyagra database, the comparator was the approximately age and breed matched animals reared on the same farms.

The question that was being asked with respect to the qualitative or quantitative differences in the adverse outcomes that were noted in cloning were done in the context of other assisted reproductive technologies. Do you want to add anything?

MR. WOOD: From our perspective we are concerned about trying to draw conclusions when comparing clones to another technology. And we find it more helpful to compare clones to the impact of husbandry systems within the general population.

So I wasn't sure how to draw what conclusions at that point. And that may be something that you want to address in the final draft.

DR. RUDENKO: Thank you.

MR. MATHESON: Dr. Craigmill.

DR. CRAIGMILL: I was just wondering if in the process of doing your data comparisons you found any cases where it was possible to compare the clone with the nuclear donor. Any information in terms of physiological, health status, or compositional factors.

DR. ADAMS: In terms of health status, the only information we have is one study that was done, it's actually a behavioral study, from the University of Connecticut, where they compared the behavior of the four clones they had to the donor as well as to age match comparators.

DR. CRAIGMILL: Swine?

DR. ADAMS: Pardon me?

DR. CRAIGMILL: Swine?

DR. ADAMS: No, these were cattle. These were Holstein cattle.

DR. DUBBIN: I mentioned that study briefly. And that the behavior was more like that of the dam. She had certain personality characteristics that were distinguishable and they showed that personality characteristic. Like, I think, reluctance to enter the barn or something like that.

DR. McGLONE: Very nice presentations. I thought they were very clear and well done. I was wondering if there

was supporting evidence for some of the statements. One of the conclusions, which I agree with in terms of general biology but I was looking for some hard data to support, the notion that gametogenesis naturally cleared the genome of inappropriate signals. Do we have any actual data to support that concept?

DR. RUDENKO: I am unaware of any molecular data to support that. The rather extensive database in mice is what we rely on. And this is one of those biological assumptions that --- stated as the front part of reviews that deal with this issue. And for which we would like to have more data than we do. But at the moment we are relying heavily on the mouse data.

DR. McGLONE: Right. And, so is it also safe to assume that because there are differences in the outcome of cloning different species that it wouldn't be prudent to use the data from one species to draw a conclusion about another species?

DR. RUDENKO: Interspecies extrapolation is always wrought with danger. I think what requires good scientific judgment and good corroborating evidence of an empirical nature is to look carefully at what the results from the model species tell you and what you observe consistently across species. But I think all interspecies extrapolation

have to be undertaken with a great deal of caution.

DR. McGLONE: Right. Then on the subject of whether it is safe to eat the product, a cloned animal or their offspring, but let's just talk about the cloned animal itself, compositional changes are one piece of information. But, have there been any studies done where cloned animal products have been fed to animals in an animal model that might indicate whether or not there are other or unknown, because you couldn't have assayed for every biochemical in the animal. So has there been any whole animal evaluation of products cloned versus convention products?

DR. RUDENKO: I am unaware of any peer review studies of that nature. And I guess I would ask you, the panel, what the relative merits of such a study would be. What would you use as a comparison? Toxicological studies are very hard to do in this kind of mixed medium environment.

And I think one of the reasons -- there is no etiologic agent. What are you looking for a difference in? And I think that is one of the reasons why we have been looking to composition to help provide some of that information. And as well as to the physiological parameters that we have evaluated.

DR. McGLONE: Well, it seems to me that if there was a compositional change, that it wouldn't necessarily

indicate there was a problem with the product. If a cloned animal produced milk with more fat, it would not necessarily be a problem.

And if it has the same amount of composition, fat let's say, it doesn't mean there is not a potential problem until you feed it to an animal, let's say, an animal model. And even if you were just looking for unexpected findings, you would learn something from doing that, wouldn't you? That would equate to the safety of the product.

MR. MATHESON: I see Dr. Craigmill writing down notes furiously over there. I think maybe he has a reply to that.

DR. CRAIGMILL: Well, I wondered if at this time you wanted to address that or wanted to put it off. As a toxicologist, I don't see any need to do the long term feeding studies when you are not trying to look at a toxic affect. We have already assumed that they are not going to be toxins expressed in this fashion. I believe that was one of the underlying assumptions at the beginning, is that the genome essentially of a food animal will not express toxins.

And I think that is a very valid assumption in this regard. Therefore I don't see any reason for a long term feeding study. Long term feeding studies are designed to look at toxins and toxicants. They are not designed to look

at nutritional factors, which I believe is the focus of this.

If you were going to do that, then I think you would have to design something different, which would be a nutritional study.

Personally, I think that the assumption that is being made here is that a healthy animal will probably produce healthy food as quite good because if there were a compositional difference that would reflect dramatically in nutrition, you would probably expect it to affect the health of the animal. And that is an assumption too.

DR. McGLONE: Doesn't the fact that there are health issues early on indicate that there might be an issue? I am not saying there is an issue. I don't think there is an issue. But, the fact that the animals have certain abnormalities at a higher rate than expected, doesn't that indicate that there is some change in their metabolism?

DR. CRAIGMILL: I would, again, looking at it as a toxicologist, rather than a developmental biologist, I would not want to make the assumption that any developmental problem was a result of a toxin or a toxicant interaction. I think there are a lot of other factors involved here.

The idea of the epigenetic differences here and expressions, they seem much more likely. And that would be more a question of quantity than it would be of difference in

the actual proteins being expressed, et cetera. It could be timing, things like that.

MR. MATHESON: Dr. Kochevar.

DR. KOCHEVAR: One of the materials that we were provided, it was noted that animals had been created by embryo splitting and blastomere transfer, for some time has entered the food chains, since the early 80's and know there were 1,400 Holsteins that were registered that have gone through that process. Is there any data at all about the disposition of those products from those animals? Any evidence that there were problems with them, or --?

MR. MATHESON: I don't think there is any evidence that there were problems. Have you seen any data? Well, there is the blastomere study, I guess.

DR. RUDENKO: There is one small study looking at back fat thickness in blastomere derived beef cattle. And there were no noted differences between those animals and their closely related sibs.

That is mentioned in the National Academy of Sciences report. We did not include it in ours because we specifically address somatic cell nuclear transfer animals. The author there is Diles, et al., D-i-l-e-s.

I believe there is also a study on milk quality characteristics from blastomere clones that comes out of the

USDA. But that hasn't been published yet.

MS. SINDELAR: Do you know if they found anything in that study?

DR. RUDENKO: No differences.

MR. MATHESON: Yes.

DR. PAPPAIOANOU: I would also like to add my congratulations to the presenters for presenting a lot of information, very detailed information in a very coherent manner. And I thank you.

I had a question that actually relates to some of the feeding issues, because in terms as I think about looking to the safety of the food, I am thinking in terms of people.

DR. RUDENKO: Can you speak closer into the microphone please?

DR. PAPPAIOANOU: Sure. My mind goes to what would happen actually when you have lots of people eating these products, which has not been part of the studies. And in some of the background reading material, one of the potential problems that could occur is there was a change in the protein, might be allergies.

And so that wasn't really addressed in terms of this data and the studies that you have presented in terms of the potential for that occurring. And I wondered if you could, if there were some information on that that was in the

studies that was not presented. Or if, again, if it's just another area where there is no information.

DR. RUDENKO: There is no specific information alterations and allergenicity of proteins that come from animal clones. You know, the FDA along with other regulatory agencies has been actively involved with various international organizations in determining just how to assay allergenicity.

And we continue to be very actively involved in that. And as information comes from those deliberations that might be useful to us in this risk assessment, we will of course use it. But much of that information, as you know, looks at comparison of amino acids, primary amino acid sequences in different kinds of protein to detect whether or not there is any homology with known allergens.

We know that milk has a known human allergen in it. And we are not talking about lactose intolerance here. But true milk allergy. And we have no expectation that the amino acid sequence of that particular protein will have changed because we are not introducing an exogenous gene of any sort.

So, again, it's a very good point. And we can make a point of explicitly addressing that. And we do in the last portion of the risk assessment. Just for limitations of time here we didn't go into the discussions.

MR. MATHESON: I would like to add though that each of these clones are one offs. So any epigenetic changes in one clone may not be repeated in another, even if they are from the same cell line. So how would you predict allergenicity to appear in a food product derived from clones collectively?

DR. NOLAN: I really enjoyed the presentations as well. One thing stuck me as far as the food safety issue is do we have any evidence that the microbial flora of these animals is different from the norm? If you have a different expression of protein, some --- of protein in the gut. Could you have a difference in numbers or types of bacteria? And these then be passed on to the offspring.

DR. RUDENKO: We have no specific information on the constituents of any receptor proteins that may be present in the intestines of animals. All I can tell you is that the information we have regarding the microbial content of these animals is indirect.

And I would like Dr. Dubbin, who I am going to put on the spot right now, to address the overall issue of whether or not we see any increase in bacterial infections in those animals. Because that is the best source of indirect evidence that we would have.

DR. DUBBIN: We have no evidence of increased

bacterial infections. And we do see evidence that they can respond appropriately. If we were to talk about, I guess, bacterial load of the gut, which is what you are essentially talking about, we do see the calves with rotavirus diarrhea. That is the normal pathogen that all calves have possibilities of succumbing to that.

But certainly that would be a good case for age and location match controls because that is so dependent on so many variables. These animals would have to be essentially raised and identical and next to each other with all the same variables and environmental variables. But I don't know that we have any data to show changes in bacterial load or response to different bacterial pathogens.

MR. MATHESON: Eric is the immune response of these calves relevant though?

DR. DUBBIN: I think it's the whole point. We are talking about receptor mediated, colonization of the intestinal tract. And I think that is what I heard you say, and correct me if I am wrong, could there be some protein change for allowing certain pathogens to colonize the gut versus those that didn't.

And all the information we have to date is that their intestinal response is identical. So we don't have information on changes there. Did that answer your question,

John?

MR. MATHESON: That was one I was concerned. Any more from the Advisory Committee? Yes, Richard.

MR. WOOD: And then following up on that, I think what the National Academy of Sciences study report was calling for additional study in compositional changes. And you asked what our feeling was on that. And I guess we will have to address that later.

But I want to follow up, go back to the original question I asked, I am concerned about and would like to hear more about the selection of using ART's as the base, actually, for a good portion of the study. And in a way that becomes the norm when yet within that norm there are great problems.

What was the rationale for using ART's as the comparative base in some of the studies as opposed to using data from the general population in the experience of birthing and growth in the general population of animals, food animals?

DR. ADAMS: What we saw as we looked through the information both in conventionally bred animals and various types of ART's is the more human intervention in the process, the greater the likelihood of problems later on.

And certainly there have been a lot of studies on

in vitro fertilization. But those have mostly been laboratory studies. It's not a widely used practice in agriculture. So in selecting comparators there was the need to do some comparisons to what generally happens in agriculture versus these questions concerning the manipulation of the embryo.

DR. RUDENKO: If I could just add a little bit to that. One of the questions we were asking was does cloning cause any new kinds of anomalies that we haven't seen before. And so in order to determine whether or not you are seeing anything new, you have to try to find, if you will in terms of technology and nearest neighbor analysis.

And the closest, the nearest neighbor to somatic cell nuclear transfer might be considered embryo splitting or embryo transfer, something where you actually have an in vitro culture period prior to reinsertion. And we thought that that could help normalize across the technologies somewhat.

So with respect to the identification of the qualitative kinds of anomalies that might be noted, we thought it was most appropriate to do our comparison to the assisted reproductive technologies, the outcomes there.

Now with respect to the actual physiological data that we were evaluating in the studies that have come

through, the reason why we chose comparator animals that were approximately age and breed matched and raised on identical farms was because that is how the data came to us.

And that is a little bit of a facile response to your question. But the reality is we work with the data sets that we have available and felt that with respect to understanding the actual physiological responses of the animals in as consistent an environmental context as possible that that would give us the most appropriate comparator.

And I think the table that Dr. Dubbin showed you where we were able to demonstrate that both the comparators and the clones showed about the same degree of variance to the reference range indicated to us that that was indeed an appropriate comparator for that set of values.

MR. WOOD: What I was talking about coming to this meeting to the neighbor who has cattle on his farm, the neatest the thing he raised was concern about genetic diversity, which is also my concern as well. And I was wondering why this risk assessment, or is it more of a risk management question, does not deal with the issue of genetic diversity and the impact of cloning on that dynamic?

MR. MATHESON: I guess I get to answer that one. It appears that it is a risk management issue more than a risk assessment because you can use cloning like these other

tools really to either improve genetic diversity or limit it.

It depends on how you use it. Just like artificial selection or any of the other assisted reproductive technologies. You can use artificial insemination to limit diversity as well. It's a tool rather than an instrument of reducing diversity in and of itself. Dr. Kochevar.

DR. KOCHEVAR: This is just a clarification. Dr. Dubbin, I think it's for you. In the studies from the cattle you mention that they had, the clones had greater than 30 percent occurrence of umbilical problems, or if you calculated it out, it came out to a pretty high number.

What is the base line for non-clones, or even the comparators from that same operation? We had some comparative numbers for things like stillbirth and death within the first year. But I never got much of a base line for that umbilical problem part of it.

DR. DUBBIN: I don't know the answer to how many comparators had umbilical problems. But I can tell you from clinical experience that umbilical problems tend to be somewhat farm specific. Certain dairies or operations have more umbilical problems than others do. Through management factors. Through some genetics. There are umbilical problems that can be genetically influenced.

So, I don't have that answer. I don't know. I

could get it for you probably. But I don't have an answer offhand.

DR. PAPPAIOANOU: This question relates to, again, I think it's largely going to be an area where there is not much information. But given that you have reviewed the literature that is out there you may have some notion of this.

If I sort out where the comparisons and the comparison groups are, if I think about this, and from a food safety perspective, it would seem that when you are looking at, given it's the progeny of clones that are for the most part going to enter the food supply, that the appropriate comparison for a cloned animal would actually be breeding stock of other livestock.

And then that their progeny, whether you are talking about clones or progeny of conventional bred animals, you would be looking for that comparison. And much of the information that was presented was on cloned animals presuming they would be into the food supply.

But if you think about long term there actually would be a small proportion of that. Most of the food would be coming from their progeny. And it didn't seem that very many studies had been done looking at the progeny of the cloned animal with these outcomes. Or, that it just seemed a

better comparison for cloned animals would be breeding stock.

I would just like to, as you survey these 500 studies, or just have thought about these questions a lot what your comments would be on just the design of the studies that were actually done in terms of being able to address the questions.

DR. RUDENKO: First, I am going to have to reclarify your question, if you don't mind. You were saying that you thought the appropriate comparator group for progeny of animal clones would be the breeding stock themselves as opposed to the terminal animals.

DR. PAPPALIOANOU: Well, the point that seemed to be made was that cloned animals, because of the high cost of their production, are themselves in general not going to be used for food, at least until their purpose, whether it's age or illness, or whatever, that the vast majority of food, the quantity of food that is going to enter the food supply would be from progeny of these animals.

And very few of the studies, it didn't seem like, I can't recall now, but very few of the studies, if any actually, involved the progeny of these animals. And then as I started to think about that it was like, well, okay, so the cloned animal, it's their progeny.

And if you look at conventional bred animals, so

clones, to me, equate more to breeding stock. And progeny to progeny in terms of food entry into the food market. And, again, you were dealing with the data that is out there.

So this is not meant to be a criticism at all. I would just appreciate your thoughts on the studies that you saw whether that approach was even considered or is this just another area that could benefit from further study.

DR. RUDENKO: I think you have raised a number of really good, very provocative points. I think first by way of clarification. We assess both animal clones and their progeny even though animal clones may not be entering the food supply in very great numbers.

It was very important to us to make a statement about the suitability of those animals for entering the food supply. In addition, we also evaluated the progeny. So, we have tried to take a look at both.

With respect to what the appropriate comparator might be and whether or not -- I think the best way I have to answer that is to feed back on the point that you made. This is a risk assessment. This comes into the middle of the development of the technology.

As such, as I said at the beginning, the papers, the information on which we had to draw were all designed to ask various other kinds of questions that did not directly

address either the long term health of the animals or the safety of food products that come from them.

Most of the papers, and when the risk assessment comes out if you glance through the bibliography, you will see the highest proportion of those studies address issues such as use of this cell type versus use of that cell type. And as the field has evolved and you look at the dates of the papers as they come along, just as that groups of papers from 1997 through 2000, really tends to address the first developmental node that we identified.

And there are some papers that address some of the other developmental nodes as these animals age. But, there are really very few papers that specifically go after the health of these animals.

And in point of fact once the investigators have determined that there is no difference between the clones and whatever they are using as a comparators, sometimes it's AI, sometimes it's IVF, there is a lack of continuity of the papers. It's not interesting. It's not publishable. It doesn't go in.

So by saying that we would limit ourselves to publicly available data, we could only use those data. Now, the overall question of if you had to design this entire universe, what kinds of studies would you use. What kinds of

animals would you take a look at is a very different answer. We have what we have to work with. And we are trying to draw the conclusions that we have based on the available data. But it's a good point and we will think about it as we go back. Thank you.

MR. MATHESON: I have an explanation for you why there are not progeny data. It's because we asked that no progeny go into the food supply. So as a result, folks have not been making progeny from these clones. So in a way we have created the situation ourselves.

DR. DUBBIN: I would like to make another clarification. Which is it's been mentioned one of the reasons we don't have data on these adult clones is because of their cost. But I think that is actually, we need to reverse our view. It's not their cost, it's their value.

The value of a brood animal is, and how long it can live and produce it's gametes, not in the quality of it's meat. But in response to your question, in conventional animals, it's the growth characteristics and the mothering characteristics. And the weight gain and profitability of that particular brood animal that it demonstrated, it was measured through its life. And accordingly, we need that information on those clones as well before we even find out what the value of their gametes.

MR. : John, perhaps we should move on to public comments.

MR. MATHESON: I think that is a good idea. Aleta, would you take care of that?

Open Public Comments

by Aleta Sindelar

MS. SINDELAR: That was a very interesting dialogue here. We have moved on to the open public comments period. And we have a number of individuals who have registered on behalf of organizations. And as I call your name and you come to the mike, will you clearly identify yourself and who you represent.

Before I start calling those who have registered for the open public hearing, I would like Dr. Waddell to read into the record an announcement from the agency.

DR. WADDELL: This is an announcement regarding the open public hearing for general matters meetings.

"Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To insure such transparency at the open public hearing sessions of the Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement, to advise the Committee of any financial relationship that you may have with any company or any group that is likely to be impacted by the topic of this meeting.

For example, the financial information may include the company's or the group's payment of your travel, lodging, or other expenses in connection with your attendance at this meeting. Likewise, FDA encourages you at the beginning of your statement to advise the Committee if you do not have any financial relationships.

If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking."

MS. SINDELAR: Thank you very much, Dr. Waddell. All right. So, the rules are you have five to seven minutes to speak. At five minutes I will raise my hand, give you five and please conclude within the following two minutes.

The first requested speaker is Mike Waner of ViaGen. Is he present?

MR. DAVIS: It won't be Mike.

MS. SINDELAR: Well, you are from ViaGen?

MR. DAVIS: I am.

MS. SINDELAR: Could you please state your name, sir.

MR. DAVIS: I am Scott Davis. And in the interest of full disclosure I am president of ViaGen.

MS. SINDELAR: So the comments that you are making are on behalf of ViaGen.

MR. DAVIS: That is correct.

MS. SINDELAR: Great. Okay. Excuse me, hold on.

(Pause.)

MS. SINDELAR: Thank you. A clarification. The floor is yours, sir.

MR. DAVIS: All right. Thank you. So, ViaGen is an --- company that combines gene mapping, --- assisted breeding and functional genomic capabilities with advanced reproductive services for agricultural animal species. ViaGen identifies economic traits in animals and designs breeding programs that efficiently reproduce those traits in future generations.

Cloning by somatic cell nuclear transfer is a powerful tool for these livestock breeding programs because it allows the generation of a large number of genetically identical animals from donors who have demonstrated genetic superiority.

The end result is the equivalent of an identical twin and the clones are not transgenic but genetically modified in any way. Cloning by somatic cell nuclear transfer offers a way for the animal industry to make rapid genetic progress in breeding programs for important traits such as disease resistance and production efficiencies that are difficult and expensive to measure.

And as a result, this technology has a potential to improve animal health and reduce waste, important objectives that have proven difficult to achieve using traditional methods.

As users of cloning technology, we fully support the FDA's assessment of the safety in food products derived from animal clones and their offspring. We have provided data to the FDA from cloned cattle, cloned pigs, and their offspring. And we will continue to do so.

We have complied with the FDA's request to withhold clones and their offspring from the food chain. And we will continue to do so. And to echo a comment that was made earlier, that is the reason there are no offspring of clones to evaluate.

ViaGen's data indicates that adult clones and their offspring are indistinguishable from animals produced by conventional means. In fact, the most remarkable thing that

we have observed about clones is that they are totally unremarkable.

In our collective experience with several hundred cloned cattle and pigs, we have not seen evidence to suggest any food safety concerns. We agree with the preliminary finding that edible products from normal healthy clones or their progeny do not pose increased food consumption risks relative to comparable products in conventional animals. Thank you.

MS. SINDELAR: Thank you very much. Our next speaker is Michael Hanson, Consumers Union.

MR. HANSON: Thank you. I do not have any financial conflict of interest with any of the companies. And I am here on behalf of Consumers Union. They are the people that publish Consumer Reports magazine and we welcome the opportunity to comment on the FDA's draft executive summary of their assessment of the safety of animal cloning.

And I have some written comments which I will hand you. There are just a few brief things I would like to say. In summary, it is the position of Consumers Union that while we believe that meat and milk from cloned animals may be safe, there presently is not enough data to reach this conclusion.

And we would ask the Agency to require such data

and testing of product of cloned animals before they are placed on the market. We also think there should be labeling.

But the few comments I want to make that we are particularly concerned about is first is FDA's continued emphasis on qualitative similarities between cloned and conventional animals. To say that problems arise but are not qualitatively different from problems in conventional animals to us is almost a meaningless statement in the context of food safety.

The problems we are concerned about most in the food safety area are problems of quantity, frequency, and incidence. Frequency and incidence of disease, of bacterial infection, of contamination with mercury, of presence of allergy causing substances, et cetera.

To say that safety problems in clones are qualitatively no different from conventional animals is therefore not particularly meaningful. It would be like saying a plant where 95 percent of the chicken is contaminated with salmonella is no different than on where two percent of the chicken is contaminated.

The problems are qualitatively the same, but quantity of intense concern in terms of food safety. And I would just point out that there are a number of studies in

the literature that have found differences between cloning and both embryo cloning and in vitro fertilization.

Some of these are in a review that Dr. Wilmut and colleagues did last year. They pointed out that the problem of hydrallantois rarely occurs in natural cattle pregnancies, but occurs at the rate of some 20 times higher for pregnancies established with clone embryos compared to in vitro fertilization. That is 40 percent and two percent respectively.

The rate of stillbirths in a study of pepper cloned cattle by Infragen that was talked about at the PEW meeting last year was 24 percent, eight out of 25. This rate is three and a half times the rate of a large study done in Canada with the Canadian Holstein heifers where two point nine percent of them were abnormal, looking at thousand of animals.

And then a study that was published by Haymen, et al., on the frequency and occurrence of late gestation losses from cattle cloned embryos found that the overall rate of live births from in vitro, from IVF embryos was seven times the rate for adult somatic clones.

That is 49 percent total success rate versus six point eight percent for somatic clones. And the figure for embryo clones was 34.3 percent. So both the success rate for

IVF and embryo cloning were statistically significantly higher.

If they look at the loss of late gestation losses, which is between day 90 of gestation and calving, that was 43 percent loss for the adult somatic clones compared to zero percent for the IVF group. And four point three percent for embryo cloning.

So there are differences in quantity is important. So it isn't just qualitative differences. They are quantitative ones.

Now, if we move, I would also point out that we are also concerned about this assumption for what you need to look at for food safety. And we would just point out that the National Academy of Sciences, they specifically requested that the Agency, as they pointed out,

"Direct effects of any abnormality in patterns of gene expression on food safety are unknown.

However, because stress from these developmental problems might result in shedding of pathogens and fecal material resulting in a higher load of undesirable microbes on the carcass, the food safety of products such as veal from young somatic cell cloned animals might indirectly present a food safety concern."

End quote.

And they then further went on to say, quote,
"There are to date no published comparative
analytical data assessing the composition of meat
and milk products of somatic cell clones, their
offspring, and conventionally bred animals.
Although several studies are in progress. However,
the Committee found it difficult to characterize
the level of concern without further supporting
evidence regarding food product composition."

So they were asking for this data. They even
pointed out that for blastomere and nuclear transfers, which
had been on the market and which were thought to pose a low
level of food safety concern, they asked for data there as
well, quote

"It would seem appropriate that the FDA use
available analytical tests to evaluate the
composition of food products from animals that
themselves result directly from DNT cloning
procedures to verify that they fulfill existing
standards for animal derived food products."

End quote.

And I note that the specific requests to look at
the pathogens and fecal material, there was no data presented

here. And we would hope that that would be presented.

Finally, with this notion of your critical biological systems, the hypothesis, that a healthy animal is likely to produce safe food products. We disagree with that. Because if that were true, we wouldn't need to have a HACCP system. Because if the animals are safe, if they appear healthy going into slaughter we wouldn't need to test for any pathogens. And that is what the HACCP system is about.

So I do think we do need to look at that. And then finally, very quickly, this is in my notes, this underlying biological assumption that these clones are normal and not any different, I think the work published in the proceedings from the National Academy of Sciences last year that found four percent of 10,000 genes were seriously abnormally expressed.

And Dr. Jaenish said, quote, "There is no reason in the world to assume that any other mammal including humans would be different from mice." Jaenish believes that genetic abnormalities will be found even in the seemingly normal animals. Some of the abnormalities are simply not fatal, he said. And he calls for, quote,

"Our results are consistent with the hypothesis that most clones independent of their cellular origin may have gene expression abnormalities

causing subtle phenotypes. Conclusions about the normalcy of surviving cloned animals, therefore, should not be based on superficial clinical examination, but rather on detailed molecular analyses of tissue from adult cloned animals."

To date such data have not been published.

Finally, in January of this year there was one other study that looked at 15,000 --.

MS. SINDELAR: Sir. In the interest of other speakers, who need to come. However, Dr. Waddell, has a question if you could take a moment for him.

MR. HANSON: Who do I leave these with?

MS. SINDELAR: You can leave them at the front desk on your way out. Thank you. Sir, excuse me. I think, Dr. Waddell, did you want to ask a question?

DR. WADDELL: Dr. Kochevar has a question.

DR. KOCHEVAR: I actually to clarifications. On the comparison between the in vitro fertilization studies, was that comparing the industry at a comparable stage of development to where clones are now? Or is that comparing IVF some 15 years after it was established to cloning, which is fairly new? That would be the first question.

Then the second question is, your comment about pathogen load studies. The previous VMAC meeting, just

before this one, there was a great deal of discussion about what is the value of pathogen load studies.

MR. HANSON: Okay. To answer your first question, the article by Haymen, et al., is in the Biology of Reproduction. It's called "Frequency and Occurrence of Late Gestational Losses from Cattle Cloned Embryos. And if you look, the IVF clones and they also did adult somatic cell clones, fetal somatic cell clones, and embryo cloning. And they did all of them here. So this wasn't data from elsewhere. They talk, if you look in the paper --.

DR. KOCHEVAR: Right. But it was data using those technologies as they exist today.

MR. HANSON: Yes.

DR. KOCHEVAR: Okay. Great. Thank you.

MR. HANSON: Yes. And I will just point out for the other thing, the National Academy did talk about pathogen loading. There could be some concern, but I think it should be looked at.

MS. SINDELAR: Thank you very much. Our next speaker is Carol Tucker Foreman, Consumer Federation of America.

MS. FOREMAN: May I use this one?

MS. SINDELAR: Sure can.

MS. FOREMAN: Thank you. That won't make the

Committee too uncomfortable. I am Carol Tucker Foreman, director of food policy for Consumer Federation of America. I have no conflict of interest.

We are an organization of 300 other consumer interest organizations, consumer cooperatives, local state and national organizations. Most of our members are like most Americans opposed to having milk and meat from cloned animals enter the food supply.

Some are confident that the perfecting of the technology will lead to ultimately to human cloning. Some are just concerned about the moral and social issues involved, ethical issues involved in cloning --- beings. Others are concerned that it will lead to the further concentration in animal agriculture. None see any consumer benefit from having meat and milk from cloned animals in the food supply.

The action last week by the FDA in issuing a press release which declared these products to be safe will certainly not reassure my members, even those who are not imposed to cloning. Make no mistake about it, the FDA's press release went all through the world as the headline, "U.S. FDA says meat and milk from cloned animals is safe."

This is a process that I ostensibly was just beginning. But the Agency almost surely has prejudged it.

Certainly in the eyes of the public. Although I think the CVM staff is to be commended for the prodigious amount of work that they have put into this risk assessment, but you have seen the possibility of real hard data.

They were completely dependent on companies to give them information. Why would a company provide negative information if they thought that it might make FDA hold back from moving ahead in approving these products?

Dr. Hanson raised the issue of the pathogen load in animals. This is of great concern to us and to the National Academy of Sciences. A healthy animal can be full of bugs that make human beings sick. And there is evidence that stressed animals shed more pathogens than others. Did anybody look to see if the fecal material from these animals have higher loads of pathogens?

The public needs data that are driven by our needs and not just those that can be provided to the Agency by the interested parties.

The Bush administration in addition has still not made a commitment to engage in a discussion of the moral and ethical issues involved in this technology, as recommended, again, by the National Academy of Sciences. Nor has anyone suggested that consumers be given the opportunity to avoid these products by having them clearly labeled in the

marketplace.

My members are not sure why FDA has felt the need to move ahead and bring this issue to you today when you don't have really any more information about this risk assessment than we do, which is an 11 page summary of what is clearly an extremely detailed document.

The data are very limited. And as the public becomes aware of the limitations, and as the debate goes on, I think it is likely that they will be even less accepting of all food biotechnology than they are now.

FDA could take some steps to reassure the public about food safety at least in this area by simply prohibiting the passing of milk and meat from clones into the food supply since we have been told that at least in the case of meat that is not likely to be essential to the economic success of the industry. I can't think of any reason why that should not be done.

And I think, in fact, for the industry's sake, it would probably be better to keep the milk out too, because I believe that the public's reaction may be entirely negative and much more burdensome than keeping it out. Thank you.

MS. SINDELAR: Thank you. Our next speaker is Joe Mendelson, Center for Food Safety.

MR. MENDELSON: Good afternoon. I appreciate the

opportunity to address the Advisory Committee and the Center for Veterinary Medicine. My name is Joseph Mendelson. I am the legal director for the Center for Food Safety. We are a non-profit organization, membership organization made up of consumers and environmental activists.

I should say I do not have any financial conflict of interest. I come here representing both our organization and our membership. Similar to the statement that Ms. Tucker-Foreman made, our organizations and members do object to the presence of any cloned meat or milk or products derived from their progeny entering the food supply at this time.

I must say the risk assessment creates significant questions for me about how this administration deals with science. And if I can digress a moment, it's a very warm day outside. A beautiful day in November. Maybe a symptom of climate change.

In the climate change arena, we have a process called the inter-governmental panel on climate change. 2,500 scientists from around the world have gathered to develop data over 15 years. Consensus documents were released every five years. And this administration still says we don't have the adequate science to judge whether we can address climate change.

And we come here today on an 11 page draft risk assessment with ostensibly one study and one new data set. And as Ms. Foreman mentioned, we have the FDA putting forward some type of draft determination on safety. Clearly that is premature. And I don't know if this administration can have it both ways. 2,500 scientists and we don't know. You know, a couple, and we do.

The issues may be different and certainly different in degrees. But it goes to the heart of what is rigorous science.

My colleagues have also mentioned that there are a number of issues that haven't been looked at. We talked about the pathogen load. It was mentioned the question of genetic erosion. That is another issue that the National Academy of Science did raise, page 50.

On the compositional data, I would say if it's a question of whether there is costs involved in slaughtering an animal, that burden shouldn't fall on consumers. That is a cost of doing business to make sure that that product is safe. So that should not be an excuse for not having that data.

I also think the Agency should start engaging in what it is calling risk management now. Our organization thinks that there should be a, the moratorium should be made

mandatory. Consumers have no reassurance that this product is not entering the market right now under a voluntary system. I am not suggesting that it is. But there is no assurance right now.

It also raises the issue with FDA should be engaged in an inter-governmental process with USDA to determine what exactly it's legal authority is to regulate this issue. Is it the animal drug application process? Is it the Animal Health Protection Act? Is it the federal meat inspection and Poultry products inspection? What is the authority to regulate this?

Because if you don't have authority to do it, or the Agency determines it doesn't have the authority to do it, then this risk assessment becomes somewhat academic.

So I would ask right now that the Agency engage in that inter-government process and release a formal opinion from the general counsel's office of FDA and USDA about what its authority is.

Lastly, I do want to get to the transparency issue. I appreciate statements made about transparency. But we have had a Freedom of Information Act request before the Agency for over a year on any data that the FDA has on this topic. And we have not gotten anything.

Consumers want labeling issues obviously addressed.

We talked about animal welfare issues need to be addressed in this process. One way in which the Agency can increase transparency is through some public field hearings, akin to the year 2000 biotechnology field hearings you had across the country.

That way you could possibly vet some of the consumer issues. I think as Ms. Foreman mentioned, you will find out what consumers' opinion really is about this issue. Thank you.

MS. SINDELAR: Thank you very much. Our next speaker is Bob Welper from Alta Genetics. Why don't you come up here and you can manage your power point.

MR. WELPER: My name is Bob Welper, and I will be presenting, as you can see on behalf of Alta Genetics. And the financial implications will be come clear through all my presentation.

Again, thanks to the CVM for allowing me to speak. And I would like to commend them for the work that they have done with the limited data that they have had to work with at this point in time.

Just to give a background on Alta Genetics, we are a marketer of bovine semen for primarily dairy. We have worked with different ART's before. As far as artificial insemination we are a developer, marketer and user.

We have been involved in the process of developing IVF, embryos from clones. At this point in time as far as somatic cell nuclear transfer, we are a user, hopeful marketer. And have worked primarily through Cyagra for our technology partner. And we have been very happy with the service we have gotten from them.

(Slide)

I want to talk a little bit about the experience that we have had with our clones.

(Slide)

We have 23 Holstein male clones at this point in time from five donor animals. The ages range from six to 23 months. And they have been under our care from ages one to six months. And they are housed in U.S. and Canada.

(Slide)

At this point in time we have had no deaths from these animals. No serious health problems. There have been a few minor health problems. One case is seminal vesiculitis which we do see in traditional animals. And one case of naval infection that ties into the umbilical challenges that they have had with the clones. At this point in time they are all healthy and growing well.

(Slide)

This is a picture of the original, or the donor of

five animals. As you can see they are all quite health and different color markings. But other than that, fairly close.

(Slide)

These are two additional clones that are housed in a different area.

(Slide)

As far as semen production, starting the precursor to reproduction, we have 15 of these animals that have been in production. All 15 have produced quality semen. Average age at first freeze is 13.7 months, which is just slightly behind the average for traditional animals.

85 percent of the production has passed quality certification. So that is above normal. Right now we produce a total of over 160,000 units that have passed quality control, so from a precursor to reproduction or fertility in the field, they do appear quite productive and higher than normal.

At this point in time, the field trial challenges, as we have talked about before with a request not to put this semen out in the field, which really challenges to generate any data at this point in time. It just sits there.

(Slide)

This is a picture of another line. Three animals housed in one location. All quite healthy, growing well.

(Slide)

Two additional ones housed at a different area.

(Slide)

As far as comparison of clones to their donors, they are very close in confirmation. Very close in semen production differences. Very close in temperament. It's amazing to talk to the people that work with them. We have one of these lines where the bull is a bit of a teddy bear, so are their clones. The other bull is not quite so nice and neither are his clones.

Small variation within the clone groups. I mean, you are going to see that due to different environments or different daily management. Less stressful lifetime production from our standpoint that these bulls are actually in production at a time when it's less stressful on them. Since we know their genetics they can be produced at a young age as opposed to an older age when they are not quite as healthy. Longevity, that is yet to be seen.

(Slide)

Example of another group of animals that we have. Again all healthy. You are seeing all the animals that we have. None of them held back.

(Slide)

Clones versus contemporaries, there really is no

differences in the care that they are getting. We have really seen no differences in the health incidence or health problems.

Very little differences in growth. Really no differences in semen production. They are producing at or above what their contemporaries are. And, again, longevity, we are gathering data as we speak.

(Slide)

Another example of clones. And just a disclaimer here. That is a camera error, they are not mutants with blue eyes.

(Laughter.)

(Slide)

Customer acceptance. I mean looking at the people that buy our product as far as buying the semen in the field. The survey results that we did a year ago were very clone friendly. That certainly there are some religious differences that people do not want to use it. But there are few that have no interest in the semen from the clones.

The main concern seems to be with genetic value of the clones versus donors that they are actually a genetic identical duplicate. And we do have continuous requests for semen from the clones.

(Slide)

Regulatory process concerns. Certainly at this point in time it's been slow in development and behind schedule. Seeing what has been done in the last couple of months and over the past year and see what was reported today certainly is encouraging.

It's limited, of course, by the available data that we have especially from progeny clones. Right now the rest of the world is watching as was stated as to what FDA and what the U.S. does. I think what the main interest, what the main impact in the food system is going to be progeny of clones, or cloned progeny.

I guess our question is how can we help to expedite the process? We have talked about limited data. And certainly there is a limitation when we can't --- progeny of clones.

So certainly we are willing to work with the government or people to develop any targeted research that we can because we are confident, if we get the data that we will show that there are very little differences.

(Slide)

And, again, I would just like to caution. We did make a lot of references to qualitative differences. We haven't made some on quantitative. But we have to realize too, that we also have said that same rules apply to normal

animals and cloned animals.

You have to realize that genetically there are differences across lines for fitness traits. So if you look at abortions, if you look at stillbirths, that there are differences in normal animals across genetic lines. So if we are going to apply the same rules, then we are going to have to start differentiating among genetic lines on normal animals. Thank you.

MS. SINDELAR: Thank you very much. Our next speaker is Karen Davis from United Poultry Concerns.

(No response.)

MS. SINDELAR: Is Karen Davis here?

(No response.)

MS. SINDELAR: We will proceed on. If she happens to show. The next speaker is Richard Nelson from the Holstein Association. You can come right to the mike.

MR. NELSON: I am Dick Nelson. I have been affiliated with the Holstein Association of America for quite a few years. Holstein Association is a non-profit organization, but we would like to break even.

(Laughter.)

It is a membership organization and so I work for the members and have no financial involvement in anything that I might say. In fact, I'm old enough that I could

retire if something happened that prompted such a move.

(Laughter.)

The Holstein Association has maintained the identification of registration slash identification records of the seed stock segment of the Holstein dairy cattle population in the United States in which over 90 percent are Holsteins.

The record organization is the largest of it's kind in the world and works to promote harmonization of animal and embryo identification and record procedures throughout the world.

This organization has maintained the records of those Holsteins resulting from embryo transfer since the first one and registered in 1974. Through 2003 nearly 359,000 animals, male/female, that resulted from embryo transfer technology have been registered.

Throughout the life of this technology there have been constant upgrading and amending of record and identification procedures to accommodate improved and advanced technology with U.S. Holstein Association staff providing leadership on an international basis. And including in that is cloning and sexing and through semen and biopsy, in vitro fertilization.

When a technician pulls a cane out of a land

nitrogen tank, it likes to know what exactly what is in the straws that contain that cane.

The impact of the embryo transfer was increased early on by dividing embryos with one-half of the cytoplasm transferred to a zona pellucida from which all cytoplasm had been removed. This was an early enhancement of embryo transfer technology.

While citing records from only 1982 through 1997, there were 1,280 females and 680 bulls registered during this time resulting from this technology, with 974 females having genetic evaluation and 189 out of 680 bulls having genetic evaluations.

While this time span is limited, this technology has been used continually from the beginning until the present with this example inserted to report there was nothing unnatural about the animals resulting from the divided embryos.

While this might be considered the earliest type of cloning, we have not regularly thought of the dividing of embryos as being a cloning procedure. The livestock industry has traditionally accepted events technology that improves efficiency or increases animal value as a matter of course when producers feel there is opportunity for improving the breed or for further financial reward.

Naturally, the acceptance of some of advancements have been met with varying degrees of apprehension. The Holstein Association began registering animals born early in 1989 resulting from transferring blastomeres of each individual cells from within a parent embryo to an enucleated oocyte.

As you know, an embryo grows from one cell through natural cell division to 16 cells in five days. But embryos for cloning may require another day or two. From March 1989 through '96, a total of 106 females and 64 bulls have been registered resulting from this technology with 70 of the females having genetic evaluations.

Therefore we have records that prove they produced successfully and created records of milk with its components as developed through regular dairy heard improvement association procedures for genetic evaluation.

This must not be interpreted to mean only 70 females matured to --- age and reproduced. As many may not have been housed with access to data collection procedure. There were no reports that these animals produced meat and milk that was not normal.

While 64 bulls were registered resulting from this technology, 11 had genetic evaluations which suggest they sired several female offspring from many different side dams,

with all steps in the process appearing normal. This does not in any way suggest that there were not a substantial greater number of bulls that were raised to breeding age and sired one or more offspring, but not a sufficient number to produce a genetic evaluation or were within a system where data was collected.

On the other hand, one must conclude that some of these animals were not raised to breeding age and were therefore slaughtered for human food. By now most of these animals resulting from this technology have gone into the food chain.

More detailed information showing dam, offspring combinations and other detail identifying animals resulting from this technology was assembled from the Association's filed by --- Robertson early in 2002, and provided to a member of the committee on defining science based concerns associated with the products of animal biotechnology appointed by the National Academy.

However, the commercial application of this technology was virtually abandoned in 1992 for a variety of reasons, though embryos continued to come out of storage until 1996. While there were apparently cases of abnormally large birth weights, there were not other abnormalities reported.

The Holstein Association has solicited and collected reports on abnormal animals since 1958. It has recognized that certain infirmities may not have been reported. During this time the animals resulting from this early technology of cloning embryos were in the general population.

Though this technology involved interaction between the nuclear material and the cellular plasm into which it was inserted, as is the case with transferring somatic cells, there were not reports of any kind to indicate any animal or person was adversely affected by the meat or milk from those animals.

Given early indications that cloning procedures using somatic cell nuclear transfer would not be considered differently, inventors and breeders of registered Holsteins implemented use of this technology on a limited basis. To date 63 females and 17 males have been registered.

MS. SINDELAR: Mr. Nelson.

MR. NELSON: Particularly in -- just a minute. Were not registered in lightening capacity for market meat. And many animals were destroyed.

MS. SINDELAR: Sir, we have your comments. That will be available on the web this evening.

MR. NELSON: All right. Thank you.

MS. SINDELAR: Thank you very much. If there is more time after everyone has had a chance to speak, Mr. Nelson, we would like you to come back up and finish if that is suitable for everyone. Our next speaker is Michael Appleby. He is the vice president, farm animals and sustainable agriculture, the Humane Society of the United States.

DR. APPLEBY: Good day. Dr. Michael Appleby from the Humane Society of the United States. I have no financial involvement with biotechnology companies. And I have to say I think it's unlikely that situation will change.

I had many years at the University of Edinburgh where I worked on animal welfare and animal ethics. And in that position I knew Dr. Welmer well, who was the man who created Dolly. And indeed I met Dolly. Anybody who would like that photograph taken with me, you can form a line at the door afterwards.

(Laughter)

On food safety, we do not challenge the Committee's conclusions with one exception. That the assumption you made that sick animals do not get into the food chain is simply wrong. There are many examples, many major problems of sick animals. Downer cows, for example, getting into the food chain. And insofar as that affected your conclusions, it's

one you should reassess.

But our main point is that food safety is not the major question that should be emphasized. We are well aware and we commend you for the fact that there are other assessments that proceeded parallel and subsequently. And as has already been emphasized the fact that the headlines are given to food safety is a dangerous emphasis given the number of other ethical questions which are obviously important.

On risk assessment, I would like to put to you the suggestion that this discussion should in fact be happening ten years hence or possibly not happening at all. The technology is clearly still an extremely experimental stage. There are very few papers to report. And there are major gaps in the data.

The conclusions are still potentially altered by a single paper. And I notice that you did not take into account the paper that is prepared in Nature in August on cloned pigs. Four pigs, one died shortly after birth. The other three died before six months old from heart attacks that would excel. It may be too recent for you to take into account. That itself would alter the conclusions of this draft summary.

Being experimental work requires review by institutional animal care committees. And the basis those

committees work on is potential costs and benefits from the work.

So let me concentrate on the potential costs to the animals. You asked have we adequately identified the risks to animal health. Well, the costs you have outlined are graphic, if occasionally considerably understated. For example, when you say the proportion of live normal births appears to be increasing. Yes, it's increasing from very, very bad to very bad.

One issue you have not covered is the unspoken assumption that there is a neutral status quo in the absence of cloning. And as has already been emphasized, the fact the costs to animals are similar to those of other technologies does not, of course, justify those costs.

And on the contrary, an area which you have not picked up is the fact that the animals being cloned are those with particular problems, such as cows with udders so large that these produce major leg problems and lameness. Very high producing animals frequently have major welfare problems from growth rates or milk production or whatever it should be.

And one reason this is not being recognized is another unspoken assumption in this case, which is heavily value laden. Use of phrases like superior genetic merit,

improved milk production, better growth rate, are value laden and assuming that production from individual animals should always be increased. And increased is the right word rather than improved.

So that is potential costs. What about potential benefit. I suggest to you that the potential benefits of this technology are none. We are already producing far more meat than we can eat in this country to the extent that the agriculture industry has to export it in order to make a profit.

We are already producing milk so cheap that it is in the supermarkets cheaper than water. Society, consumers, do not need this technology. The only benefit that would accrue from this technology is to biotechnology companies.

And it could well be that the people who will benefit from this technology number less than three figures. We could be talking about this being introduced for a handful food benefit of a handful of people.

The conclusion of any reasonable cost benefit analysis is this work should not be proceeding and that is why I say that this discussion should at least taking place in some years in the future and maybe not taken place at all.

We commend the precautionary approach being taken by the FDA. But we would warn against the expectation that

this moratorium will soon or indeed ever be lifted. And in view of the major problems to animal health, we are very concerned that the lack of appropriate mechanisms for control other than a voluntary moratorium.

There is a strong feeling here that we are on a down escalator which has no break. We would urge the FDA in parallel with its other assessments to look urgently into mechanism for installing a break on progress on this technology. Thank you.

MS. SINDELAR: Thank you very much. We only have a few minutes here. Are there any others who are interested in providing a brief statement from the public?

MS. FINELLI: My name is Mary Finelli. I am here as a concerned citizen. I have no conflict of interest with cloning technology. And no interest in it either. Except to oppose it. It's known to cause pain and suffering.

In an October 31st article in the Washington Post entitled "FDA says cloned animals are safe food" states

"The technology is plagued by high failure rates, spontaneous abortions, and severe health problems in many clones and their mothers."

It goes on to state,

"Cloning problems are worse in some species than others. They are notably severe in cows, the prime

targets for firms working on commercial cloning."

In the FDA's own press release, it states, "The adverse outcomes may occur at a higher frequency with cloning than with other assisted reproductive technologies."

For the same reason it is immoral to clone humans in that it entails unnecessary pain and suffering, it is wrong to clone other animals. They too experience pain and suffering. The public is opposed to animal cruelty, which cloning involves. And the government should in no way support or promote it.

In its report on cloning last year, the National Academy of Science panel also pointed out that animal welfare is a serious concern. The government is on one hand urging the public to eat less animal products, it is contradictory to endorse a process that will make animal products more readily available.

I ask that any public outreach effort that the FDA undertakes regarding cloning should make it very clear to the public that cloning causes animal pain and suffering. Thank you.

MS. SINDELAR: Thank you. Are there any other comments?

(No response.)

MS. SINDELAR: Is Karen Davis here?

(No response.)

MS. SINDELAR: Okay. I think this closes our open public comment process. And we will take a break and return at 3:15.

(Whereupon, a brief recess was taken.)

MS. SINDELAR: --- and begin with the VMAC deliberations. If everyone can have a seat please. I would like to thank Dr. Sundlof and his speakers for staying up here for the rest of the deliberation process here such that the VMAC members will be free to address them with any questions. So at this time I would like to hand the baton to Dr. Waddell, the chairperson.

DR. WADDELL: Oh, yes. If I may, we had just finished up public comment prior to the break. And to be fair to all the speakers, we cut one off. And I would like for him to come to the microphone and finish his statement before we begin deliberations.

MR. NELSON: I am sorry. I apologize for taking more time that was allotted. And I sincerely appreciate this opportunity. All I would like to say is that we have many, a few entrepreneurial breeders or registered dairy cattle that want to be on the cutting edge of leading technology, who have invested five figure dollars from 40, to 50, to 60, to 80 and \$100,000 in animals that are clones. And who are

anxious that these animals and their offspring are such that the meat and milk from them and their offspring can enter the food chain and that it not be labeled. Thank you.

MS. SINDELAR: Thank you, Mr. Nelson. Thank you, Dr. Waddell.

VMAC Deliberations

by Dr. John Waddell

DR. WADDELL: Okay. We will begin our deliberations. And the questions are posted on the screen. And what we will do is I will read the first question, and we will go around the Committee and if each Committee member could give their comments and how they will address each question.

So the first question to VMAC is,

"Based on what we have been presented, has the risk assessment adequately identified the hazards and characterized the risks relating to animal health?"

So, Dr. Craigmill, would you begin?

DR. CRAIGMILL: As a toxicologist, as I was explaining early to Dr. Sundlof, I have little difficulty using the term risk in this regard because when I look at risk I look at quantitative information. I am not sure we have real good quantitative information in this regard to actually come up with a risk.

I do appreciate very much the fact that we are talking about a qualitative risk assessment here and looking at the differences and trying to identify unique problems. There are some data in terms of the risks to the animals. I

believe the FDA has done an excellent job in characterizing what information is available.

In that regard, as to whether it answers the question definitively, I can't really say that it does. But I think it answers it definitively to the point that it's not an area where a whole lot of additional study needs to be done other than to collect information on the ongoing process and what is currently underway.

So I think current, if we collect more data on what is actually going on now, I think we can elucidate this question a little bit later.

DR. WADDELL: Richard.

MR. WOOD: I don't think we do have the data that is needed. Where there is data, it's identified clear health problems, particularly in the earlier nodes of development. I think we also, the risk assessment needs to reassess the tension that has been identified between qualitative and quantitative issues in the risk assessment.

For example, if the number of calves that die on a post-natal period is doubled, is that a qualitative difference, and questions of that nature that were also raised in some of the public testimony.

I mean, overall I think that would be my general comment about the risk assessment as was noted and said very

forthrightly by all the presenters today, is the lack of data. And it would be helpful I think to learn what the strategy is for accomplishing the wish list that was alluded to in one of the presentations.

So my view of what we have is an interim risk assessment and that is okay. The technology is developing so the assessment perhaps needs also to get underway and to review the studies that do address the questions at hand as they are apparent.

A separate track that goes beyond both of these that I feel a need to mention, even though it was referred to earlier as perhaps a risk management strategy, but I think it needs to be addressed because perhaps the motivation for moving ahead on the risk assessment is to in some ways be out in front of the developing technology on cloning.

And that is the need to define regulatory authority. And as a consumer representative, I thank the industry for voluntarily withholding the marketing of their products even at some loss, I am sure, to them, while there is regulatory action.

But I do think that attention and time needs to be addressed in defining that authority and taking, or taking the legislative steps necessary to achieve that authority. I also think as was mentioned earlier by one of the

commentators from the public that a larger forum should be called together.

Perhaps as a risk management step and maybe risk management at this time, if that is that step, needs to happen at the same time as risk assessment that would involve the USDA, FDA, and perhaps others. A model could be, and not a clone, because it's certainly had it's failures. But the administration's task force on food safety that was a larger gathering of interested parties and stakeholders around this question. Or perhaps even the ethical and religious questions that underpin some of the questions that we are dealing with today could also be addressed.

So my answer to the first question is that the data is not there to provide a sufficient risk assessment. I do thank the FDA for acknowledging that and taking the data sets available to begin the process of a risk assessment. But that is yet to come.

DR. WADDELL: Dr. Pappaioanou.

DR. PAPPATIOANOU: Thank you. My answer to the first question also is that with what was presented that there is not sufficient data to be able to answer the question. There are very few studies at best. Most had incredibly small sample sizes. If one even --.

Many of the statements that were made was there

were no differences noted. You just wonder if they calculated the power of that what was the probability of finding a difference if one existed. I don't know. You know, five, ten, 15, 20 percent. It's just hard without a power calculation there.

I understand the difficulty of the endpoints that they were trying to contend with. But nonetheless I think the data with that regard makes it almost impossible to be able to answer the question.

New studies are needed. I take heart and absolutely believe in a risk assessment or a research synthesis effort. That one of the big values from doing that is to identify the data gaps and to guide the research that is needed to answer the questions.

And I would think too that with what we have heard too with considerable money going into the development of this technology that some resources could be found to do those studies and to get that data. That would allow a clearer picture as to be able to be able to answer the first question. Thank you.

DR. WADDELL: Dr. Wages.

DR. WAGES: Thank you. Clearly the cloning issue is a powerful technology that at least personally I see the potential benefits far outweigh the risks. However, if you

look at the answer to the first question as it is proposed to us, it's difficult to answer that question, yes, with the data that we have been given.

If you look at it qualitatively in clone versus uncloned, if you will, animals, I think there was a decent job in the information presented that anything happening in the cloned animals also happened at least in some percentages or some aspect in the uncloned, or the partners, if you will.

However, the majority of the data is in cattle. And you have a lot of other species in question that are just not there to make a decision on. I think when you have information that was presented today with limited data -- and I want to interject. If you are an anti-cloner, you are never going to get enough data. There is never going to be data to support cloning. So I think to go to that aspect, it's never going to happen.

There is always going to be a gap in the data if you don't like what is being presented. However, I think you can look at trends even in small numbers. And I would think even with the breeding that was done in the cloned animals, you at least got some impression that there were different hazards that would be coming apparent versus, you know, the uncloned animals. And it just wasn't done.

Everything that occurs, even though there is an

increased quantitatively in some of these, like hydrops, ---, those clearly do occur in the normal population. However, to straight answer the question, I think there is still enough lacking information to where I don't think I can assess where all of the hazards have been adequately identified.

DR. WADDELL: Dr. Parkhurst.

DR. PARKHURST: Thank you. I think you are trying to tackle a very, very difficult issue and clearly, as everybody said, and as you, yourself, said the data set is very, very small. But you have to start somewhere.

And in that spirit, I would say that you looked at what you have and you started to make categories. And you said that as age became, as they became older well then they started to even out. The problems that were there started to even out.

And so that is a beginning. In my view you also looked at it and you didn't identify any catastrophic events. I mean you can at least say so far we haven't come across anything that is catastrophic.

And you are starting to build a data base, which is no small thing. In looking at the summary of values that you have here both in the chemistry and the hematology, you have different parameters. And looking at those parameters I think you gave a nice picture of the numbers and where they

are going.

I do think a power assessment would be nice, you know, given the numbers that you have. And what you think a meaningful difference would actually be. That would need to be specified.

And you started. You have looked at it in a uni-variate case. You are looking at it a one variable at a time which is the way you begin. But then we all know that these variables are correlated. And the more they are correlated, then we have to take that into account when you talk about the picture as a whole.

And looking at whether these are all part of the same population would be, you could take this to your statistician and talk about influence points and whether they truly are part of the same picture. It's just much harder to see as you get into multi-dimensions that are going on.

So I think you have made a start. And you just keep having to say over and over again the way you did that this is just the beginning. It's a very small data set and we have to be very, very careful about making any conclusions whatsoever.

DR. WADDELL: Dr. Jack.

DR. JACK: Ditto is probably too easy an answer to give. But, I tend to agree with most of what my colleagues

have said. As you described yourselves, this is an iterative process and not to belabor the point, but it's a good first step.

I think many of the hazards have been identified. I think the characterizations of the risks of the data is just lacking at this point. So it's hard to say. Based on what we have been presented, yes to both of those questions. I would say at best, it's a start. The answer can't be given at this point.

DR. WADDELL: Dr. Nolan.

DR. NOLAN: Thank you. Ditto, again. Well, I am a bacteriologist. And what strikes by what you have been doing is, you know, I can study a million sub organisms in a single mill. And you are studying a very complex organism and its very, very difficult to do. I never lack for data. You have to struggle with the other problem.

So I guess where I am is I feel like we could use some more data to be able to answer this question. At the same time I recognize how very difficult it is. Thanks.

DR. WADDELL: Dr. McGlone.

DR. McGLONE: I would like to commend the FDA again for putting together a complex set of data in a qualitative manner. I think the answer to the first question is clearly no. That we don't understand enough about the risks to

animal health.

And I would encourage the FDA to think about the issue of cloning as they might think about a drug and cloned animals are not a drug. But in that they ought to develop a plan for what information might be needed and then execute that plan in an expeditious manner.

And include in the animal health evaluation animal safety and something that might be termed animal welfare. I know you don't like that mandate. But I think there is not a lot of difference between animal safety and animal welfare.

And what I would be looking for as a scientific reviewer is some data that already exists, but more data on behavioral comparisons of cloned animals, their relatives, and non-relatives, on physiology, endocrinology, and immunology of the three set of animals.

Of diseased challenged animals whether they would be differently, whether their clones, and their relatives and non-relatives would be different in response to disease challenge, which would include food safety studies.

And, finally, with all of those data in hand, then you could and you should and you could even begin a quantitative risk assessment to animal health that would indicate the increased risk to morbidity and mortality, behavioral changes, physiological changes and so on based on

comparisons.

And it's not to say that if there is a two fold increase in mortality, for example, that that would necessarily mean that it wouldn't be a reasonable technology that would be acceptable under some circumstances.

So, the last challenge, I think, is that for the country, is that there are a lot of apparent critics of cloning. And there are advocates of cloning. And perhaps the two groups should get together and fund the studies. Because the studies that are needed are in the general interest of the country and the world and not only unique to individual corporations.

So I think a little cooperative planning and execution of the studies that I described would give comfort to the consumer that the animal health is being protected. Thank you.

DR. WADDELL: Dr. Kochevar.

DR. KOCHEVAR: I would start by saying that I think the FDA had done a very good job of creating a system in which more data can be added and rationally assessed. And the two components to that are the care with which you look for comparators to your clones that are meaningful. And the creation of the five node system whereby you are not comparing for the most part apples and oranges. You are

comparing animals within a group.

I think with that system in place and the wish list that you have provided, the track to getting the data you need will be faster than what you have had to date. That as you said there are inherent problems with publishing some of this data, so some of it has just not been done.

That said, I think when you look at the data that you have looked at for cattle that I think you are approaching the point where you have adequately evaluated the risk to animal health. I think that you have an end that if you did the power analysis on, you would probably be close to being where you need to be.

In addition, I think it's very hard to know where the base line is on this stuff. That if you took 500 completely normal animals and looked at the incidence of the things you are trying to quantitate in these clones, there would be as much variability there as there is in the clones. And so I mean you might just collect data forever and not really ever have a compelling conclusion to it.

So, at some point I think you have created the framework to be able to make a rationale analysis. I personally am compelled by the bovine data because there are much higher numbers represented there.

And I guess the final piece is that this intuitive

sense that if you have done embryo splitting, you have done other assisted reproductive technologies, we obviously have natural occurrence of 20, that none of those represent apparently risks to -- well, now I am on question to two. Risks to the consumer.

But, overtime have also not presented compelling risks to animal health. Then I would suggest that you are approaching at least with cattle the point where you can say, yes, you have adequately assessed that risk.

DR. WADDELL: I too believe that it's a very good first step. And I mean, this technology is in such a infancy stage that we have to start someplace. And I think if you really look at question one, on just it's own merits that a risk assessment has identified the hazards. And characterized the risks.

And compared to some of the other ART's, that were mentioned today and even were developed prior to that, we have already gone off a lot further with this issue and this technology than what we did with those. And so I think it is a good first step. And I realize there are tons of data to come yet. So I think the answer to number one is yes.

Okay. We will move on to question two.

"Based on what we have presented, has the risk assessment adequately identified the hazards and

characterized the risks relating to food consumption?"

And we will start again with Dr. Craigmill.

DR. CRAIGMILL: Just briefly. I think the answer is yes. And then I will fill in why. Again, it's very difficult to do an actual risk assessment on this other than a qualitative look at the possible hazards that might exist. And when I talk about a hazard, again, it's a possibility, it's not a probability.

I think if you looked at this scientifically, there is really little reason to expect that there could be a problem from this. Seeing as how you are taking a nucleus from one cow cell, or sheep cell, and putting it into the cell body of another cow or sheep cell and you are just transferring genetic information, it's all epigenetic.

There is nothing new added there which would add any new toxins or potential proteins which would add new allergenicity problems.

In terms of the expression of proteins, that is a difficult question to answer. That is certainly something that could likely occur in the clone. It seems very unlikely in their offspring.

So in brief, I would just say that I think they have done an excellent job on this and support the

recommendations that have come out.

DR. WADDELL: Mr. Wood.

MR. WOOD: In response to this question, in one of the first pieces that came out anticipating this event, somebody from the industry said, I think it was Mayor Times, quote "Is there a strong and impressive body of scientific evidence that will convince consumers that this food is safe?"

And that is a general question. Not a specific question that is before VMAC, but to that, I think the answer is still no. And looking more specifically at the second question and looking at what has been provided, there still is insufficient data in our view, my view, that regarding the composition of cloned bovine meat or milk, although a great stride has been taken in the direction regarding bovine meat with the Cyagra data.

And it would be great to validate that with other data. I said in a break to somebody, I said, how many studies does it take to say that we now have something this scientifically valid? And I am sure that is a question that is open for debate.

But there is still insufficient data as far as I am concerned. Because not enough of the data on milk from clones, as was identified in the risk analysis in its

executive summary. There is not enough data on the safety of pork, swine meat. There is no data on sheep clones.

So, that to me says that there still is not sufficient data upon which to take this step. And to respond to one of my colleagues here, it's not as if there never will be enough data on this question. I think that we are moving in the right direction.

And you have been encouraged by others to look at pathogen load. I think that is an important focus as well. And you asked whether or not the composition of food should be further examined. Then I think you ought to continue that focus as was called for by the National Academy of Science report.

So I don't believe that meat or milk should be approved from clones at this time as a result of this risk assessment. Nor should the meat or milk of progeny until there is further review.

Also, the issue of labeling has been raised by one of the comments. And that certainly is a risk management step that, if there was approval, would allow consumer choice.

DR. WADDELL: Dr. Pappaioanou.

DR. PAPPATIOANOU: As before, I really do commend the group in terms of the risk assessment that was done and

very much appreciate the constraints that they faced on the limited data. You can only do so much with what you have. And it was a very fair look.

However, again, some of the issues in terms of lack of information on several of the species. The desire to lurch into the expression of proteins and potential outcomes from that, or possible impacts on the intestinal flora in terms of overall as animals would go into the food supply, which is really where the rubber would meet the road, that is definitely deserving of more investigation.

Many of the assumptions and the biological hypotheses put forward are very believable. They make all kinds of sense. But, as I kept asking myself as I was actually looking at the data that was being presented, I didn't see where the data began to lead me to a confident answer.

And I am not one, I work in public health. We are used to making lots of decisions based on incomplete data. But it's easy to say well we will never have enough data to basically, with 100 percent confidence, be able to say that this is safe.

And that is true. There is nothing that is 100 percent. But one can generate data, studies that give more confidence and that does relate to the design of the

study, the quality of the study, how the studies were conducted. How many animals were in the study.

And one can then come to a conclusion that if you come up with a quote, unquote "negative finding" of there is no difference, that you are at least 80/85/90 percent confident that you can believe the negative results.

So, again, my overall conclusion is that, no. Based on the posture of data, clearly not the model that was set forth or the process. But a good beginning as others have said, with hopefully the research agenda that comes out of this that can begin to be addressed to fill those gaps and to answer the question affirmatively. Thanks.

DR. WADDELL: Dr. Wages.

DR. WAGES: I am a little more comfortable with this question than I was with the first. Even though there may be some data lacking in both of these questions.

When I look at potential for food safety, there was a variety of blood chemistries and blood values that were given in comparing the cloned versus uncloned animals. Or the comparators, if you will. Up into the 99 percent comparable to the comparative counterparts.

And I think if you look at, especially in the cattle data, if you will, I think if you look at, again, trends, I think with the numbers that we at least observed in

cattle, I think if there was something that would come up from a nitrogen retention, some type of physiological problem that has the potential of affecting quality of meat or milk. I think it would have come out.

One think I would have like to have seen in the milk studies at least is butter fat content, even though that varies. Depending on diet it does give us a sense of the electrolyte or at least the acid based balance of the dairy cow. And if there are any changes there.

I am reasonably comfortable that the food consumption portion of the cloning issue, I think we have identified the potential hazards and the answer to that question would be yes.

I think one thing that would solidify even things more for me would be I think there is a lot of universities that would just be tickled to death to get these cloned progeny, food science departments, and pick these guys apart. And actually provide some of that final data in carcass quality and even analysis of meat or milk.

And that might be something that could be very, very useful to put more of an end to some of the questions or speculations on the quality of meat. So, yes.

DR. WADDELL: Dr. Parkhurst.

DR. PARKHURST: Thank you. Again, I would have to

say I don't know. I don't see that there really is enough data. But I do think that in your presentation you have presented a well constructed design as to how you could get more data.

And, in fact, I thought that that was some of the things that you were asking for. You said in general there is just so much variation in the whole population that we consider normal. How can we go about and get something on cloning animals that would be any different.

And one thing I would suggest is to look at the analysis of variants components. That is a study in which you would be able to see if they came from the same population or if there was something different along those lines. That is the biggest thing I have to say right now.

DR. WADDELL: Dr. Jack.

DR. JACK: Thank you. Again, I think I am going to fall in line with most of my colleagues. I believe that a lot of the -- I tend to feel that the evidence or my sense of what is going on with the risk assessment for food, I feel a little bit better about that than the risk to the animal health.

So that is if these animals are living to maturity or getting to a point where they enter the food chain that a cow is a cow is a cow. That you are taking the nucleus of a

normal healthy animal and sticking in another cell.

I guess my concern though is that we don't have much data on the progeny. And if those are the animals that are really going to enter the food chain, we really need to take a look at those.

And, again, my intellectually, it would seem a fair assumption that the progeny shouldn't be changed at all. But we don't have any evidence to show that one way or the other. We just don't know.

So, you know, based on the assumption that the offspring are like the parent, we are in good shape. But it's still an assumption.

DR. WADDELL: Dr. Nolan.

DR. NOLAN: Thank you. Well, based on the data presented and on the rationale assumptions on which their interpretation were based, I don't think there is any reason to assume that the milk or the meat from these clones or their progeny will be unsafe.

But I do feel uncomfortable, often and unqualified, yes. Again, like many of my colleagues here, I think it would be good to see more data. And I would especially like to see data on the progeny since they are the ones likely to enter the food supply.

I think it's an interest, something we may want to

see addressed is the microbial flora of the clones and their progeny. Thanks.

DR. WADDELL: Dr. McGlone.

DR. McGLONE: On this question, I think based on composition data, that the answer to the question is yes. That the cloned animal is functionally similar in composition. But I think, qualifying my yes, that in this case the consumer wants more.

The public wants more. And in fact in this case science at the moment cannot deliver that. The consumer has the fear of the unknown of things that might be in the meat that are not yet described, perhaps.

And the only way to confront that from a science point of view and move on is to actually do the studies where when products are fed. And not only where they are fed to normal animals, but also to animals at risk and to young animals, neonatal animals, because people have a fear of what goes in the mouth of their children. And any other member of the population that might be at risk, perhaps people that are sick or elderly.

So to go an extra step in this case, I believe, is required. More so than if it were normal food stuff that doesn't have any consumer hot button attached to it. So in this case I think we need some data that go one step beyond

what would normally be required under these circumstances in order to develop the confidence. So that we don't lose the confidence that the consumer has in our food supply. And we can in fact culture it and nurture it and help the animal industry satisfy this consumer desire for animal products.

DR. WADDELL: Dr. Kochevar.

DR. KOCHEVAR: I think that one of the slides that was shown pointed out that until this fall no, zero peer review publications relevant to SCNT on --- were available. And then the Walsh study was then looked in some detail.

I think those studies are the direct evidence that you need to be able to answer yes to number two. I think you have abundant indirect evidence. And that evidence is, again, back to the bovine data set.

You had such high percentages of sort of concordance between the clones and the normal animals. 90 percent, 99 percent in that. That the reasonable expectation is that these animals have those parameters that similar and obviously function normally in terms of being able to emulate and reproduce and various things. Then it is a reasonable assumption to say that they are not going to be a danger in terms of the food supply. That is all indirect evidence, though.

And so truly if you had to have direct evidence,

you really would have to do some of the studies that you mentioned on your wish list. I don't think those should. I mean those kind of studies seems to me would not take an overwhelmingly long period of time to do. Those are basically meat composition and milk.

They are confounded by the variability in normal milk and the meat. But, except for that caveat than those studies seemingly should be fairly direct. And I do think that data would be very useful to support the argument.

DR. WADDELL: Again, taking the question in its face value, and what we were presented earlier today, I would have to answer yes to question number two also. And echo many of the comments from the rest of the Committee as far as the data. But, I think that it is coming. The thing is coming. But we, you know, have to make the first step somewhere along the line.

Are there any other comments from the Committee?

(No response.)

DR. WADDELL: Hearing none, that concludes our deliberations.

MS. SINDELAR: Dr. Matheson will take over for the concluding remarks and next steps.

Concluding Remarks and Next Steps

by Mr. John Matheson, Moderator

MR. MATHESON: For those of you that have been patient enough to stay all day and are victims of the Advisory Committee who have had to stay all day, we thought we would treat you with about ten or 15 minutes about where the next steps are in reaching a decision.

Again, not being specific about particular risk management options, but to explain the difference in how we look at them.

(Slide)

This is a repeat of what you saw this morning. It's our goals. We are still trying to reach a science based decision. And I think we are accomplishing some education about cloning. And we are still reaching for a risk management process that is proportionate to the level of risk.

(Slide)

You saw the spin diagram in Dr. Rudenko's presentation. But if you imagine these tubes as a three D structure and turn it on it's side.

(Slide)

The point being that a risk assessment does not

automatically lead to just one risk management option. Many risk management options can be perfectly consistent with the data you have in the risk assessment.

That is the next stage in this process after we get past the risk assessment. So many options are possible. I think you heard some suggested during the afternoon.

(Slide)

Does the risk assessment or what we have discussed today change CVM's position on food derived from clones or their progeny? The answer is no. This is just the science portion of the process. So only through risk management would we change the policy.

Would there be any change in the position? Some of the risk management actions that are available to FDA include things as simple as guidances for industry. Policy statements. Regulations. Even compliance policy guides which are instructions to the field for how to inspect.

(Slide)

A few words about the risk management process itself. This is the stage where burden comes into place versus the benefits. And the tolerance for uncertainty from the risk manager's point of view. What level of uncertainty are you willing to live with?

Enforcement issues become important. Can you

enforce any policy? How can you enforce it efficiently? How about in international trade? What are the consequences for noncompliance?

These are all non-science issues really. These are things that come in when you start talking about risk management options, and the role of other public and private groups. It has been mentioned there is USDA at the slaughterhouse to consider and we have been coordinating with them; by the way; and also private groups like Dick Nelson's group; and other breed registries for example. What is their role in tracing, following clones and their progeny?

(Slide)

No policy is ever final. Final guidance are always open for comment, continuously. And they are monitored for effectiveness, especially where there is concern that there may not be something working or that there may be some changes in the technology that will change the effectiveness of the guidance.

(Slide)

And then there is also communicating. So a word or two about risk communication. Not only to our stakeholders here in this meeting in the U.S., but you may have noticed there are a number of people in the audience from Canada. And we have also met with folks from Australia, Japan, the

U.K., Italy, France. They are trying to reach the same decision that we are trying to reach. We are all faced with this technology and trying to make a rationale decision about it.

There is also an OECD project underway to look at cloning, and the food safety. And we will be participating in that later this month.

(Slide)

And the place where we will be updating folks on a regular basis is our website. We encourage you to keep checking there. And we have a special biotechnology page, which now has a cloning sub-page so to make it easier for you to find.

With that we have a few final words from Dr. Sundlof, who would like to wish you well. Thank you.

DR. SUNDLOF: Thank you, John. And I would just like to thank all of the folks who came and participated in this. This is an extremely important issue not just for FDA and the Center for Veterinary Medicine, but obviously, it has much broader ramifications. And your input is very valuable to us in making those difficult decisions.

I especially want to thank the Committee. To kind of step into FDA's shoes for a day and try to make some of the difficult judgment calls that we are required to make

every day.

And just as we do, you see that there is not a unanimous consensus among the members. And that is very representative, I think, of population as a whole. So I think we have impaneled our Committee very well to represent those diversiti4es of opinions.

Again, your recommendations and your counsel will be very valuable to us as we proceed forward. As John has indicated there will be additional information coming out. We are right in the middle of the process. And it's good to have everybody along with us for the journey because it's a, as you have seen, it's not an easy path to walk.

But, again, I want to thank John Waddell serving as a very able Chair again. John, thank you. And thank you to the members of the Committee. And all have a safe trip home. Good night.

(Applause.)

(Whereupon, the meeting was adjourned at
4:10 p.m.)

