Public Meeting: Incorporating Alternative New Approaches in Clinical Investigations for New Animal Drugs

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P R O C E E D I N G S

(8:30 a.m.)

Introduction

by Walt Ellenberg, Ph.D., Special Advisor, Office of New Animal Drug Evaluation

Center for Veterinary Medicine, FDA

DR. ELLENBERG: Good morning and welcome. I would like to welcome our distinguished guests, industry stakeholders, folks from academia, private citizens and fellow FDA staff.

I am Walt Ellenberg, and I am a special advisor to the Office of New Animal Drug Evaluation in FDA's Center for Veterinary Medicine. Thank you for coming.

Today's meeting will address four primary areas on matters involving incorporating alternative approaches and clinical investigations for new animal drugs. Unlike other agency meetings in which the outcome of the meeting is delivered in the form of a recommendation to the commissioner, this meeting is different, and it provides stakeholders the opportunity to introduce new ideas, perspectives, data, approaches on various issues to FDA for consideration.

In other words, this is the perfect time for you all to submit information to us for consideration as we move forward in the development of guidance. It is important for

me to remind you that this is a public feedback meeting, and as such FDA will be participating only in a listening mode. And remember that the questions and the presentations and the discussions that you hear today are not necessarily indicative of the FDA's position on the matter, nor do they forecast future directions in the regulatory development of these particular areas.

In fact, one of the primary goals of this meeting was for us to cast a broad net in order to optimize the diversity of information that we receive and are able to consider.

However, before we begin, there are a few things I need to address. The first item focuses on today's agenda, and you should all have a copy of it because it was available in the lobby. You will note that there are two sessions in the morning, two sessions in the afternoon. Each of the sessions, each of the paired sessions, is actually, will be separated by a break. The breaks will serve as transition periods during which those individuals who will be participating in the subsequent panels and/or speakers will come down and make sure that they are ready to go five minutes before the conclusion of the break or five minutes before we resume from lunch.

Each of the actual sessions will consist of a topic-specific presentation and/or panel discussion. Please

note that the biographical information for each of today's speakers and panelists is available in the lobby on hard copy. This information is also available on the Web.

In keeping with the public meeting designation, each session includes time for an oral presentation from the public in advance of the meeting. FDA received several requests to speak at the open session. As such, speakers have been scheduled to talk during the appropriate session.

At the instructed time, the scheduled speaker will be invited to the podium to give his or her presentation, and the speakers are reminded that when they do approach the podium, would you please state your name, your affiliation -- I apologize for the feedback. We don't know where it is coming from honestly, and that is the truth, but I am going to continue.

Please note that the transition from session to session will occur during the breaks. I just mentioned that but I wanted to repeat that. To avoid delays, speakers should find their way down here before we start because the schedule for today's meeting is very, very tight.

We hope that the panel discussions and presentations will trigger additional ideas and perspectives. As such, we want you to take the time to submit information to the docket for consideration. The docket number, which has been rotating on the screen in front of you, is FDA-2019-

N-2281. This docket will remain open for comments and other information until August 17, 2019.

As a reminder, this meeting is being Webcast, and should we encounter a Web-related problem, potentially what we may be hearing right now, we will do everything in our power to correct this. So please understand that we still will move on during the meeting. If there is a problem with the transmission of the Webcast, that will not prevent us from continuing with the meeting because this meeting is being transcribed and the transcribed information will be available not only on our Website but it will also be submitted to the docket so you will have the opportunity to see it.

And so finally I would like to ask folks to check your phones, make sure that they are on mute so we can begin. So at this time, I would like to get the meeting moving. And I invite Dr. Steve Solomon, our director of the Center for Veterinary Medicine, to make his opening remarks.

Opening Remarks

by Steven Solomon, DVM, Director, Center for Veterinary Medicine, FDA

DR. SOLOMON: Good morning, everybody. We welcome you to today's public meeting. Excited to see so many of you in person, and welcome those of you that are on the Webcast. We are very fortunate today to have as our opening speaker Dr. Ned Sharpless, the acting commissioner of the Food and

Drug Administration since April 2019. He previously served as the 15th director of the National Cancer Institute.

Prior to his appointment at NCI, Dr. Sharpless served as the director of the University of North Carolina's Lineberger Comprehensive Cancer Center, a position he held since January 2014. Dr. Sharpless was a Morehead scholar at UNC Chapel Hill, received his undergraduate degree in mathematics and went on to pursue his medical degree from the UNC School of Medicine, graduating with honors and distinction in 1993.

He then completed his internal medicine residency at the Massachusetts General Hospital and a hematology oncology fellowship with Dana-Farber/Partners CancerCare, both at the Harvard Medical School of Boston.

After two years on the faculty of the Harvard Medical School, he joined the faculty of UNC's School of Medicine in the Department of Medicine and Genetics in 2002. He became the Wellcome Professor of Cancer Research at UNC in 2012. As you will note, his career has focused both on alleviating the suffering caused by cancer and promoting research into promising new therapies. It is my honor and privilege to welcome Dr. Sharpless.

(Applause)

DR. ELLENBERG: For those who are attending over the Webcast or maybe on phones, please mute your phones

because we are getting a tremendous amount of feedback and cannot hear the speakers. Thank you.

Comments

Norman E. "Ned" Sharpless, MD, Acting Commissioner, FDA

DR. SHARPLESS: Good morning. Thank you, Dr. Solomon, and let me add my warm welcome to today's public meeting. It is my pleasure to help kick off what looks to be a really interesting topic and set of discussions.

As stated, my prior role prior to becoming commissioner of the FDA, I was director of the National Cancer Institute at NIH since 2017. And before that I spent 20 years in academia as a cancer researcher and cancer doctor treating patients with hematologic cancers. As NCI director, I really was focused on --

(Technical feedback)

What an exciting time it is to be a cancer researcher because the pace of progress in that disease has been so remarkable. And now that I am at FDA, it is thrilling to be involved in areas that go beyond cancer as we advance our public health mission across the spectrum of human and animal medicine.

As a physician and cancer researcher, I have seen the positive impact of scientific innovations on patient health, and advances in science are changing the trajectory of so many areas of public health, which is why I am excited

to be here today to discuss how we can continue to support and promote innovation in animal drug development.

I also have experience with the private sector, which has given me an appreciation of the opportunities as well as the many challenges from both the developer and the regulator perspective when it comes to new medicines. I have learned in my short time at FDA that the Center for Veterinary Medicine is a real microcosm of the FDA, regulating a truly fascinating portfolio of technological innovation.

As an example, intentional genomic alterations or IGAs in animals have tremendous potential to improve nutrition, address animal health disease issues, produce substances for novel drugs, help prevent the spread of zoonotic diseases and yield tissues and organs for xenotransplantation. And this is an astonishingly rapidly developing field, and CVM is really at the forefront of its implementation for the public health.

The center is also committed to fostering innovation of new animal drugs with implementation of its new authority for expanded conditional approval, something we will probably talk a lot about at this meeting, to treat certain serious or life-threatening diseases or conditions or to address certain unmet animal or human health needs.

We are really excited to see this program later

this year when we put out more information clarifying the eligibility criteria for the expanded conditional approval pathway. CVM scientists are also at the forefront of using new models to reduce, replace and refine the use of animals in research through the development of innovative bioequivalence studies.

And in the last few years, we have seen animal drug approvals that not only brought new treatment options to veterinarians, animal producers and owners but also showcased innovative approaches to meeting the regulatory requirements.

For example, through a combination of government-sponsored aquaculture research and publicly available use data collected in natural outbreaks of disease, a new indication was added to the label for Parasite S, a formalin product used to treat fungal disease in freshwater-reared fish, finfish.

Another example is the use of a novel study designed to assess the prevention of lyme disease in dogs. Studies that measure the transmission of Borrelia burgdorferi to dogs after exposure to infected ticks supported a novel indication for NexGard for the prevention of Borrelia infection in dogs by killing the vector ticks before they transmitted the infection.

While we are doing a tremendous amount of excellent, innovative work across the animal sector, I do

believe we can do more. If we want to harness the full potential of animal drugs and animal feed to transform the industry in animal health, we need to become more efficient, more collaborative and more data driven so that we can learn from every patient, every animal patient's journey and utilize all available scientific data.

To fully and effectively achieve FDA's mission to promote and protect public health, we must seize the opportunities offered by these scientific and technological advances. The Animal Drug and Animal Generic Drug User Fee Amendments of 2018 provided FDA the opportunity to engage the public on different approaches to modernizing clinical trials in veterinary medicine in support of animal drug developments.

Consistent with that charge, we will discuss today how to incorporate the following principles into clinical trial protocols for animal drugs. So complex, adaptive and other novel investigation designs, data from foreign countries, real world evidence, biomarkers and the use of surrogate endpoints.

The User Fee Amendments of 2018 highlighted the role foreign data might play in FDA's evaluation of Food Additive Petitions. The session today on data from foreign countries seeks input on how these data can inform FDA's evaluation of both animal drugs and animal food additives.

Some of the questions we might ask ourselves today include: Can complex, adaptive and other novel investigations designs make trials more flexible? How can we better utilize data from foreign countries to support animal drug approval and Food Additive Petitions in the United States?

What approval steps are needed to truly support a global approval? And I should mention that we are fortunate today to have with us Dr. Mary Jane Ireland, Director General, the Veterinary Drug Directorate of Health Canada, who will be speaking on international regulatory collaborations, so thank you for being here this morning.

How can real world evidence be used to maximize the available information for the evaluation of safe and effective animal drugs? Real world evidence may include ongoing surveillance activities, observational studies and registry data among other things.

Our speakers from private industry and academia today offer two perspectives on the use of real world evidence in animal drug developments. We look forward to their input on how we can harness these data to support regulatory decision-making, and this is, you can imagine, a topic permeating throughout the FDA presently, beyond CVM.

How can biomarkers and surrogate endpoints be identified, qualified and applied to the effectiveness

evaluation of animal drugs? There are many other questions we will need answers, to ensure the FDA is taking an appropriate, well-informed and science-based approach to the design of clinical trials for animal drugs.

It is also important to reaffirm, as we work to make our process more efficient, and as we look forward to the new technologies and new methodologies, we will always maintain our focus on the FDA's gold standard of efficacy and safety. And that's both target animal safety and human safety.

As explained in the background materials for today's meeting, there are several existing guidance documents already available on the topics under discussion today. You could ask why we don't simply apply these policies to animal drugs. As you participate in today's meeting, and as you submit comments to our open docket, consider the unique challenges of animal drug developments. The large and varied number of animal species, different housing types, and many animal management and husbandry practices.

Consider how we can leverage the existing knowledge and experiences with human drug development and apply them in the most appropriate way to animal drug developments. Your feedback and most importantly your ideas can offer us new pathways forward. We look forward to your

comments and your proposals to overcome challenges that can move innovative products to approval while maintaining FDA's public health mission.

I thank you all for taking the time to join us today and for your contributions toward these important topics. And have a great meeting.

(Applause)

DR. SOLOMON: Thank you, Dr. Sharpless. Let me take a little bit of a step back and just reinforce some of Commissioner Sharpless' points. As we mentioned, this specific public meeting came about during the user fee reauthorization that occurred last August. Specifically in the Animal Drug User Fee Act, Section 305, Congress instructed us about guidances addressing investigational designs.

CVM is to issue guidance or guidances that will help sponsors incorporate complex, adaptive and other novel investigation designs, data from foreign countries, real world evidence, biomarkers and surrogate endpoints into proposed clinical investigation protocols and applications for new animal drugs. Specific language in the statute.

This applies to new animal drug approvals under Section 512 of the Federal Food, Drug and Cosmetic Act. And also to conditional approved new animal drugs for minor uses or minor species under Section 512. 571, sorry.

We also are supposed to address how we will evaluate these investigation design elements in our regulatory review process, and how sponsors can get feedback from us on technical issues related to them before submitting an application.

We are here today to consult and hear from you, our stakeholders, including regulated industry, consumer groups, academia, veterinarians and food producers. The people that are in this public meeting, both here in person and those on the Webinar, we want to hear from you in the purpose of this meeting.

After this meeting, we have a year to digest all of the information we've heard and the information submitted in the docket that was talked about before, and issue either a draft guidance or guidance documents.

There will be a public comment period on those draft guidances, and then we are to finalize the guidances a year after that. So we have a tight timeframe of a lot of activity so this meeting is critical to get that input.

There is another section of the Animal Drug User Fee Reauthorization that is unrelated to veterinary pharmaceuticals but very much dovetails with the charge to promote innovation. Section 306 addresses food additives intended for use in animal food. It amends the Federal Food, Drug and Cosmetic Act by requiring us to review reports of

investigations conducted in foreign countries as part of our process for reviewing animal food additives.

As we were planning this conference, we thought it would be advantageous to include the discussion of food additive foreign data since we are already covering foreign data in the pharmaceutical arena.

So that covers the statutory basis for the meeting but tody's meeting is not perfunctory in trying to meet a statutory mandate. It reflects CVM's strong support and commitment to investigating these critical issues, and which we expressed during our discussion with Congress.

So during the negotiations, we talked to them about the need to look for innovative new approaches, re-examine how we are looking at the process of approval of drugs.

As you well know, we have a philosophy and approach in CVM to engage with sponsors early in the review process to establish the most efficient and relevant process for conducting clinical investigations.

As Dr. Sharpless noted, it has already resulted in many examples of innovative ways to achieve new animal drug approvals using alternative approaches. We all recognize the challenges of availability, of safe and effective animal pharmaceuticals. The range of diversity of species that we are dealing with -- food-producing animals

ranging from bees to dealing with wildlife and elephants.

Real challenge in CVM in trying to get veterinary pharmaceuticals available. The wide spectrum of animal disease conditions and evolving animal production conditions.

In addition to the organizers, we have nearly 150 CVM scientists and other staff attending today both in person and on the Webcast. I think this demonstrates the level of interest of the Center for Veterinary Medicine in these topics and our interest in your perspectives on these issues.

I welcome and encourage you today to take part in a robust dialogue today, and also to make sure you further provide comments to the docket. We have put together an outstanding agenda and speakers and panel participants.

We are pleased to have representatives from our FDA colleagues from the Center for Drug Evaluation and Research and from our Center for Biologic Evaluation Research who have been looking at these issues from the human medicine side, and who we believe their insight will be invaluable to us.

We also have outstanding representatives from the National Institute of Health, industry, academia, consultants and our regulatory partner of Health Canada's Veterinary Drug Directorate.

We welcome additional input from today's discussion since we all recognize that the best ideas come

from collective thinking and dialogue. So this is the start of that discussion. You could also provide your thoughts and potential solutions to the docket, which is open until August 17. So I remind you of the importance of that.

Before I turn the floor over to our first panel, let me thank the organizing committee that put this meeting together. This is not something that we do on a routine basis so they went through extraordinary work to try and put this meeting together.

I would like to recognize the lead organizers and the section coordinators and ask them to stand when I mention their names. Susan Storey, Walt Ellenberg, Lisa Troutman, Jean Recta, Phil Turfle, Emily Smith, Ana Lazo, Amey Adams and Chris Louviere. Thank you.

(Applause)

I would also like to thank many other people in CVM who contributed to this event, from participating in the technical committees, helping at the registration desk, helping with travel planning, helping in the parking lot to make sure people could find the location. So there are a lot of people involved. I would also like thank Barbara Cruze and Tom Flood and the Johns Hopkins University for their willingness to accommodate our needs in holding this public meeting. We could not have fit you all into CVM.

Finally I would like to thank all the

participants whose contributions are making this meeting possible. I will be in attendance in the morning, and apologize but I need to leave for a meeting in DC this afternoon. Believe me, I would much rather be here with you all. So let me turn this meeting over, and I look forward to the good ideas coming forth. Thank you very much.

DR. ELLENBERG: Hi, everybody. This is Walt Ellenberg. We are going to go off script for a second. I need to ask for those who are participating online via the Webcast, I would like for you to know that we understand and acknowledge that there are audio problems that are going on, on your end and you may not be able to hear us with great clarity. But please know that we are working on it.

And so I would ask that you refrain from raising your hand or clicking or toggling any of the buttons because it is showing up in the middle of our screen. So if you would refrain from that, I would appreciate it but we are working on the sound. Thank you.

(Applause)

Topic 1: Complex, Adaptive and Other Novel Investigation Design

Introduction: Lisa Troutman, Veterinary Medical Officer,

Division of Therapeutic Drugs for Non-Food Animals

Center for Veterinary Medicine, FDA

DR. TROUTMAN: Good morning. It is my privilege today to kick off the first session of four sessions on

complex, adaptive and other novel investigational designs. I want to thank Dr. Sharpless and Dr. Solomon for their opening comments in welcoming everybody here.

So as I said, I am Lisa Troutman. I am a Veterinary Medical Officer in the Division of Therapeutic Drugs for Non-Food Animals at the Center for Veterinary Medicine. So as you heard, the purpose of today is to seek feedback from you. We want to hear from you and help gather feedback to issue a guidance document a year from now on these topics. And there will probably be multiple guidance documents.

(Slide)

So in fall of 2018, the Center for Drug Evaluation Research and the Center for Biological Evaluation Research issued a guidance document on adaptive designs for clinical trials of drugs and biologics, and this was specific for human drugs.

There are other guidance documents that have been issued such as adaptive designs for devices. There have been enrichment strategies. There are two specific for oncology drugs. There are master protocols. There are expansion cohorts. And also one for devices for Bayesian statistics.

(Slide)

So we put together a set of three questions that we are seeking feedback on, and if you are not able to

provide feedback today, we do encourage you to provide feedback to the docket, which will be open until August 17th.

(Slide)

So our first question is how do we apply these guidance documents to the study designs for animal drugs? What are the potential study adaptation features that we should apply to veterinary medicine? What challenges and possible solutions do we have to apply these adaptive designs for veterinary medicine? And what types of studies can we use for our study designs?

(Slide)

Our second question is more along definitions. What is an adaptive design compared to a complex adaptive design? This was a question posed to us from Congress. What constitutes other novel investigational designs? And what are examples that are directly applicable for us, for veterinary medicine?

(Slide)

Our third set of questions is are there partnerships that can be formed between FDA and the regulated industry, academia or other groups to facilitate the development of these novel study designs? What strategic work is needed to enable the regulated industry to make full use of these novel investigational designs? And what methods are needed, such as simulations or modeling, to help

facilitate the use of these designs?

(Slide)

So CVM has had some experience with adaptive designs. We have used sequential designs for sample size re-estimation for blood level equivalence studies. We have used it with sample size re-estimation and protocol designs. And in pilot studies we have seen dose escalation studies that are using a sequential approach.

(Slide)

So again we greatly appreciate your feedback. We are in a listening mode today and so we want to get as much feedback as possible. We are privileged today to have a wonderful panel of specialists that I will introduce. We have two people who are going to be speaking: Dr. Robert Temple from CDER will be speaking on his experience in developing these guidance documents on adaptive design.

Dr. Aloka Chakravarty is going to be speaking from CDER on a pilot program that they have clinical investigational designs. They are then going to join the rest of the panelists that we have up here. We are privileged to have Ms. Margie Bell, who is a statistician with animal clinical investigations, and she has been involved in many study designs and worked with many companies. We are privileged to have her.

We have Dr. Dottie Brown, who is with Elanco

currently. She used to be at the University of Pennsylvania, and she has been involved in a lot of study designs and adaptive designs, especially with pain models.

And then last but not least we are privileged to have Dr. John Scott from CBER who has also been instrumental in developing these guidance documents that I pointed out previously. So without further ado, I am going to invite Dr. Temple up to start his presentation.

(Applause)

Invited Speaker No. 1

Robert Temple, MD, Deputy Director for Clinical Science,

Center for Drug Evaluation and Research (CDER), FDA

DR. TEMPLE: Good morning. As will be apparent, I have almost no information about studies designed to show effectiveness in animals. So how applicable this is all going to be, you are going to have to decide.

What I am going to tell you is the things we have done over the years. I should also note that I didn't correct every error on my slides, including the first one, because it should have said novel designs, not drugs.

(Slide)

As was mentioned, we put out a guidance on adaptive designs that has a million suggestions. It is 25 pages in great detail. And some of them are so simple, you

would have thought people would do it all the time.

For example, there are free adaptations, things where you look at the total population not by treatment group and test whether your assumptions are right. Are the baseline characteristics distributed the way you hoped? Are the outcome event rates total overall not just in the treated group the same? Is the measurement variability similar? And you can adapt those things, and you don't pay a statistical price for those. They should sort of in some sense be done all the time. And that seems clear.

Another thing not always done is that one can continue a trial until a certain number of events are achieved. That seems far more sensible than assessing the sample size right off the bat. And yet that is not commonly done and it should be. And it is certainly the sort of thing that can be considered.

(Slide)

There are other fairly obvious things to do. It is perfectly sensible to look at interim effectiveness results, statistically corrected using various things are well-known, group sequential designs analyzed by the O'Brien Fleming method or Lan-DeMets. There are lots of them. And if you are not very sure about how things are going to come out, how big the effect is, there is some statistical price for doing this but it is the sort of thing that should be

considered all the time.

It makes sense to consider adaptations of sample size. One can do an interim effectiveness evaluation. They don't usually contemplate changing sample size but there is nothing that says you can't. And in territory where you are not familiar -- a new animal species or something where you don't have a whole lot of data, it makes tremendous sense to do that.

There are also possibilities for adaptive enrichment not commonly used. One could examine subgroup responses and adjust the population or analyses or randomization rates of different subgroups in humans, including more males or more females or something like that, again with control of Type 1 error. But if you don't consider these things, you won't get to do them.

(Slide)

The other big thing, and I am going to spend most of my time talking about this, is the possibility of enrichment. In some sense that is an adaptation taken before the study. It is to choose a population that is one way or another is more likely to be able to show you that the drug has an effect than not. It will do that for the particular population you studied.

(Slide)

It might raise generalization issues but it does

succeed in showing you that the drug has an effect in some population. We have detailed guidance on this, on how to select a population for study that is particularly likely to have the outcome events of interest. That is called prognostic enrichment. Or is especially likely to respond because they have a genetic or pathophysiologic characteristic. That is called predictive enrichment. And again, I am going to talk a little bit about how this can be done in human studies, and you all are going to have to decide which, if any, of these maneuvers could be useful in the animal study world.

(Slide)

So what is enrichment? Enrichment is the perspective used, perspective now, of any patient characteristic, whether it is demographic, pathophysiologic, historical, genetic, lots of others -- behavioral -- to select patients for study to get a study population in which detection of a drug effect is more likely because they have something to detect.

And this occurs to a degree in every trial. There is always entry criteria, although the idea of enrichment may not be explicit. And there are three major things you try to do. One is to decrease heterogeneity, noise of various kinds. I will give you some examples, whether any of these are applicable to the animal world I am

not sure but you can see.

As I said, the second is finding a population that has a lot of outcome events. High-risk patients. That is prognostic enrichment. It tells you about that population but at least it's a place where you can show at least for starters that the drug works on somebody.

And then identifying a population capable of responding to the treatment. That is predicted enrichment. Far more common as we now begin to understand the genetic and pathophysiologic causes of diseases. It is becoming much more possible to do that, very strikingly in cancer. Essentially almost all cancer drugs are targeted in a particular population. Now that did not used to be true.

As I said, lots of examples in here. You will have to think about how many seem applicable to the animal world.

(Slide)

Okay, the first kind -- again, whether this is really applicable, I am not sure. But the first thing you have to do is reduce heterogeneity and noise. So in clinical trials we're very careful to define the entry criteria carefully. You don't want to put someone into the trial who doesn't have the disease you are trying to treat. Duh, that is fairly obvious.

In humans, you look for likely compliers. I am

not sure if that is a problem with animals. You will have to say whether it is. My favorite example is a VA hypertension study done many years ago in the late '70s, I think, where they had an open period in which they included riboflavin in a placebo. And when you shine a light on someone's urine with riboflavin in it, it glows.

So they treated all the prospective people with a placebo, and if their urine didn't glow, they didn't randomize them. I mean, this was done a million years ago. It's a very good idea. No point in studying patients who won't take the drug.

You try to choose people who won't drop out because of concomitant illness or because they can't get to the clinic. You try to eliminate placebo responders in a lead-in period, a very good idea.

You get rid of people who can't do the test. If there is a treadmill test, and they vary up and down over the placebo period, don't put them in the trial. You are not going to be able to see anything. There is going to be too much noise.

You eliminate people who have a concomitant illness that is going to make them drop out of the study or die. And you take out people who are already on the drugs. So that's easy.

(Slide)

Apart from practical enrichment, which I just described, enrichment comes in two flavors. One is prognostic enrichment. Again, you will have to figure out how this applies to the animal world but you are trying to find high-risk people, those who are likely to have the study endpoints you are trying to reduce. Or is likely to have a large change in the endpoint being measured, a high rate of deterioration or something like that.

And how to detect that is often tricky. It has major study size implications of course. In humans, at least, the size of the effect matters. You would be more impressed if the drug has toxicity of 50 percent change in event rate. It would mean a lot if that is what you have got in high-risk patients. You might accept considerable toxicity.

So it is important to know that stuff. Again how that applies to the animal world, I don't know.

And then the other kind of enrichment, as I said, becoming extremely important as we understand the genetics and pathophysiolgy, is choosing people more likely to respond to people. This could be proteomic or genomic. Could also be patient history. It could be identification of an early response on a biomarker.

You only randomize the people who have tumor response, things like that. You could do those things. Or

an early radiographic measure, something like that.

(Slide)

Again these are human examples. How well these are going to apply, I don't know. The information distinguishing individuals with respect to risk is growing rapidly. We understand these things much better but we've had that sort of information before. An example is looking at cardiovascular outcome studies.

We know that having heart failure makes you more likely to have a wide range of cardiovascular events. Having high cholesterol or high blood pressure or angiographic abnormality -- those all predict people who are going to have trouble.

The presence of diabetes means a greater likelihood of heart attack. Having had a recent event heart attack or stroke recently, elevated C reactive protein, a study of a lipid-lowering drug or super statin in people with minimally elevated cholesterol was successful because they picked people who a high C reactive protein, which predicted a high rate of response, a high likelihood of having a heart attack.

So you took people -- they were therefore able to show a benefit in people with only modestly elevated cholesterol, not a trivial matter.

I am not sure how much this applies but cancer or

previous breast cancer is a good predictor of having contralateral cancer. So if you are doing a study to prevent the development of cancer, you might want to pick people who already have one to see if you can do another.

And as it says there, tumor histology or genetic proteomic markers can predict occurrence of metastases and that kind of thing.

Prognostic enrichment is critical in any test where you are trying to prevent something. They better have the event or you are not going to be able to prevent it. So you know that, and I already gave you the contralateral cancer case. I won't dwell on that any further.

In cardiovascular medicine, it's long been routine to try to pick people at high risk, and it can be unbelievably successful. My favorite example in heart failure was a study of an ACE inhibitor called enalapril in what is called the Consensus study. It's hard to show survival benefits is cardiovascular outcome studies. They have to be very big. There will be thousands of people.

(Slide)

The Consensus study was done entirely in New York Heart Class IV people. That's people who can barely get out of bed, okay. It included 253 patients. Not 4,000, 5,000, 6,000. It showed a survival effect in only 6 months and that's because the untreated mortality was 40 percent in 2

months.

So the fact that the drug worked was easily demonstrable in this study, and then they did later studies in people with less severe illness. But getting the very sick people is a very good example.

The first lipid outcome study was the 4S study of Simvastatin. That was done in people who had had a heart attack, very high cholesterol. Had a 9 percent 5-year mortality. Showed a survival advantage. Later studies had much more difficulty showing that.

So enriching with people who have the events is a good idea.

(Slide)

And as I said before, probably the most exciting enrichment strategy that people are thinking now is predictive enrichment, finding patients who are most likely to respond because they have the genetic marker that the drug affects, things like that.

These are going to be all over, and I am not going to dwell on them too much but -- I am not going to give the examples. They are human examples but you have got to see whether there are, in fact, animal examples of the same thing, people with a marker that predicts they will have this disease or something like that.

(Slide)

And of course the pathophysiology of the particular disease can matter as has been known for 50 years. Hypertension can be high-renin or low-renin, and high-renin population will show a much larger effect to drugs like ACE inhibitors, angiotensin blockers or beta blockers because they work by inhibiting renin function.

We study antibiotics obviously in people with the infection sensitive to the antibacterial, and more and more genetically determined differences can be the basis for pathophysiological things. And I am not going to give examples but this is mostly in tumors and things like that. ER positive tumors respond to certain drugs and not others.

(Slide)

People have done those things in the past, even when they didn't understand the genetics. One of my favorite examples was something called the CAST study a million years ago, which was trying to see if people could respond to antiarrhythmics. That is, if antiarrhythmics would prevent mortality.

So they took a bunch of people who had had at least 10 ventricular premature beats after having a heart attack because it was known that those people had a higher mortality rate. And the first thing they did was screen with a couple of very effective antiarrhythmics, and they only put people into the trial if they had a 70 percent reduction of

ventricular premature beats during the screening period. Only responders.

These were very powerful drugs, encainide and flecainide. So it was a brilliant idea but the study failed. It didn't show a benefit; in fact, it showed an adverse effect but it was brilliant idea.

Beta blocker heart attack trials in -- beta blocker trials in congestive heart failure were carried out only in people who could tolerate the drugs. Some people don't tolerate a beta blocker. They don't like the slow heart rate or they go into heart failure. The trials were done only in people who could tolerate them, and they showed effectiveness in heart failure if you could tolerate them.

It is worth noting that every randomized withdrawal study, which I am going to describe in a moment, has the characteristic that you only put in people who seem to be responding to it so it is selected for responders.

(Slide)

The advantages of predictive enrichment -- there is a table written by Rich Simon. If only 25 percent of the people, lower left there, have the marker that you are interested in, the genetic marker, whatever it is, the sample size ratio is reduced by a factor of 16.

If you put only those people into the trial, it is an enormous advantage, and you have to be thought of. You

know, it is sort of obvious. If only 4 percent of the population can respond to the drug you have, you are going to need a very large study to show anything effective. In fact, you won't ever show anything.

You would only do it if you find the responders and put them in trial. I mean, that is sort of obvious but it is very important to think about.

(Slide)

I do want to mention one study design that isn't used as much as it probably ought to be. It was actually invented in 1975 by a Belgium doctor named Amery who was very worried about the trials, the angina trials, they were doing. They were eight-month trials, and he really -- or six to eight month trials -- and he really didn't like the idea of keeping the people with angina on placebo for six to eight months. That seemed cruel and unusual to him.

So he designed a trial, designed in which you first screened for apparent responders. You gave the drug to everybody and watched them four weeks. And if they seemed to have a response, you kept them on it for another while.

You then did a randomized withdrawal. That is, you assigned some of them to continued therapy and others to taking the drug away. And for most drugs, whose effects are short-term, you got an answer on whether the drug worked in the apparent responders within a couple weeks.

So you weren't putting people on long, unethical placebos for a long period of time. And he really liked that design. And in fact it is now commonly used in a lot of situations. Many of our pain studies now use this because it is hard to keep people in an opiate study on placebo. You know, they have pain. They are not going to be in your study for two weeks and it takes that long for the thing to work.

So a lot of those trials are now randomized withdrawal studies. And the trials have another advantage. They are enriched with people who are doing well on treatment so if only a fraction of the population responds, this finds the fraction and tests them. It's a very effective way to do studies.

Another attractiveness is -- I don't know whether this is true in the animal world -- but in the human world you will often find people who are already on drugs that are being tested. There is a big population of them. Well, you can just put them to in the randomized withdrawal trial. You don't have to scout around to find patients, and they are extremely efficient. And it's a very interesting design to think about.

(Slide)

As I said, it's efficient. The patients exist and are known. It's attractive ethically because as soon as the failure criterion is met, you can stop it. It makes it a

very attractive design for pediatrics. Nobody likes the idea of keeping people on ineffective therapy for a long period of time.

(Slide)

And my final slide is you all know far better than I do -- not for better, far better -- whether the subjects of your trials can be chosen and identified, using these approaches, and if they can, it can clearly help. And I think that is something you need to think about. Thank you.

(Applause)

DR. TROUTMAN: Thank you very much. I want to just make a couple of comments. If you are on the line, please mute your phone. There is a lot of extra noise that people are hearing, and it is making it hard to hear the speakers.

The other thing I do request is for the speakers to please speak directly into the mic so that the transcription can pick it up. Apparently they are having a little difficulty picking that up.

So thank you very much. And without further ado I want to invite Dr. Chakravarty to come up and speak about the pilot program for clinical investigational designs.

Invited Speaker No. 2

Aloka Chakravarty, Ph.D., Acting Director, Office of Biostatistics

Center for Drug Evaluation and Research (CDER), FDA

DR. CHAKRAVARTY: Good morning. Can you hear me right? First I want to thank the organizers for inviting -- this is a parallel experience that I think can be of mutual interest.

So I am going to talk on our experiences on the complex, innovative design pilot, and I present this on behalf of the entire working group. I am Aloka Chakravarty, Acting Director of Office of Biostatistics in CDER.

(Slide)

So first, why? Of course, to ensure the safe and effective therapies for patients. Also CID, as I will short-form the complex, innovative design, provides a path forward for challenging problems benefitting -- for innovative thinking. One size does not fit all, and this kind of brings that to the fore. And then learn collaboratively.

In the PDUFA VI, which is the equivalent User Fee Act, there was a section for enhancing regulatory decision tools to support drug development and review. And it particularly called out complex, innovative trial designs and that includes complex adaptive, Bayesian and other novel clinical trial designs with a particular focus on designs requiring simulations to determine the operating

characteristic such as Type 1 error or other.

(Slide)

So what are the features? There can be many different kinds of designs. For example, use of historical control patients, seamless adaptive design where you are doing as maybe a dose-ranging study and then picking up the winners to move directly into phase 3.

Hierarchical modelings, use of formal trial distribution, response adaptive randomization and so on.

(Slide)

Now to the what. So the objective is to facilitate the advancement and use of complex innovative design. And to do that, there were multiple things that were put in. The first one was to develop staff capacity. The next one is to conduct a pilot program, and I am going to talk more about that in the following slides, focusing on it.

Convene a public workshop just like this one. We had a workshop about 18 months ago in April of 2018. Publish draft guidance just as CVM is tasked to do. Develop or revise relevant MAPPs, SOPPs and other review templates.

(Slide)

So let me go a little bit more into the pilot program now. This started with a Federal Register notice in August last year. And it called out the highly innovative trial design for which analytically defined properties -- for

example, Type 1 error -- cannot be possible and simulations are necessary to determine trial operating characteristics.

And this highlights the goal of facilitating and advancing the use of complex adaptive vision and other novel clinical trial designs.

(Slide)

So the CID pilot program is a joint CDER and CBER effort, and in this pilot program, the sponsors did the designs and have the opportunity to engage with the regulatory staff on designs via two meetings, two additional meetings.

The agency selects up to two submissions per quarter, and uses the design as case study for continuing education and information sharing. So this is the disclosure piece. Even before the drug is approved, this particular pilot program allows us to disseminate what were the elements of the design so that there is a very robust learning experience and you can learn from the successes as well as the failures to see, okay, we tried this, and this didn't work. So maybe we need to think about it in a different way.

The meetings are led by OB and CDER with participation for all relevant disciplines, and it's a five-year duration.

The Website is given here and I urge you to go into it and look. There is a plethora of information in it

along with a lot of details in it, and this shows quite a bit of parallelism in what CVM is undertaking as well.

(Slide)

So to be eligible for this pilot program, the sponsor must have a pre-IND or an IND number, investigational new drug number, for the medical products included with the intent of implementing CID in the pilot program application.

The proposed CID is intended to provide substantial evidence of effectiveness to support regulatory approval. The trial should not be a first in human study, and there should be sufficient clinical information available to inform the proposed CID.

And the sponsor and the FDA should be able to reach agreement on trial design information to be publicly disclosed. So the sponsor has to agree that to be in this pilot program, FDA is able to discuss some of the design elements and these disclosures are done on a mutual discussion basis.

(Slide)

So now to look at the timeline, I am going to go through this a little bit in detail. So the first one is the sponsor submits the information, then -- it's not very big so you may have difficulty in reading it. And I am having difficulty in reading so I will make a move to this side so I can read it slightly better.

So FDA evaluates the CID request. And then at the end of that, on Day 45 FDA notifies if the CID request has been accepted or not.

So if it's accepted, then FDA will -- is there a pointer I can use? So FDA and the sponsor can discuss the design elements and the disclosure elements. At the end of that, on Day 80 or thereabouts, FDA sends the meeting granted or meeting denied letter to the sponsor. And then shortly afterwards, the sponsor submits the CID meeting package.

So as I mentioned, there are two meetings, and I am going to go into the details of both the meetings because the requirements and the need for these two meetings are slightly different.

Then after that, continuing on the review path, around Day 120 the CID first meeting happens. And based on that, the sponsor submits the second meeting package, which is additional information and additional details that is needed to evaluate.

And Day 240, the CID meeting, the second meeting, happens. So that in a nutshell is the timeline.

(Slide)

So the CID meeting request actually needs to have adequate information so that we can evaluate whether that particular design is appropriate in that situation. So to have that, of course you have the product name, the IND name

and so on but a background section that includes a brief history of the development and the status of product development, trial objectives and brief rationale for the choice of the proposed CID.

The description of the study design, including the study schema, with treatment arms, randomization strategy and endpoints also need to be submitted.

(Slide)

In this package, the key features of the statistical analysis plan should be there, including a simulation plan. And it should talk about the elements of the study design that the sponsor considers nondisclosable along with the rationale for exclusion.

A list of issues for discussion with FDA about the specified proposed CID approach for the applicable drug development program and summarized list of next steps that are needed for the regulatory decision-making along with any supporting data relevant to the discussion.

(Slide)

So we are still on meeting one, and at that point, after that, the FDA evaluates the CID meeting request and particularly the trial design appropriateness for the pilot program, the therapeutic need, the level of innovation in the trial design, the value proposition of the CID, and the need for simulation to assess trial design operating

characteristics.

So as part of that, as I mentioned, FDA and sponsor discuss the disclosure elements. And the disclosure elements may include the study and points to the degree necessary to describe the design, trial population, sample size and power determination, the hypothesis, the null and alternate, key operating characteristics, assume weights for the dichotomous outcomes.

Or, you know, mean variance for continuous simulation objectives, scenarios, assumptions and modeling characteristics. And critical design elements including any adaptive elements, and if Bayesian approach is used, how Bayesian methods are being used for design or analysis purposes. How prior is chosen, discounted and what Bayesian decision rules should be considered.

So the first meeting has the proposed agenda including the time estimates, the discussion questions and most importantly the detailed description of the statistical methods, the simulation results and the overall conclusion including a brief summary of the simulated operating characteristic based on the features and analysis and discussion of the utility of the CID given the simulation results.

(Slide)

So moving on, the second package of course are

going to have much more detail that need to be discussed because these were based on the feedback that was received during the first meeting discussion.

So we test the updated background session and updated programs or shells for simulations if applicable. And oftentimes there are a few elements that need to be discussed more if it is a Bayesian design. What are the characteristics that we have to look for?

(Slide)

So here is a case example. This was actually the first one that was submitted to the pilot program. And we can discuss this because it was publicly disseminated by the sponsor.

So it was submitted by WAVE Life Sciences during the first quarter, and it was for treatment of patients with Duchenne muscular dystrophy. And in OB, the Division of Biometrics I, and OND, the Division of Neurology Products, were primarily involved in evaluating this.

(Slide)

So according to the sponsor, the CID incorporated placebo augmentation using a Bayesian modeling strategy. And an interim measure of commensurability between the historically untreated patients and the placebo data from the pivotal study will govern the extent placebo augmentation and the potential adaptation of the sample size and randomization

ratio.

So this may accelerate the availability of the effective treatment for this devastating disease and reduce the number of patients required in the trial.

(Slide)

So I just wanted to acknowledge people who know about this much more than I do. Dionne, John Scott right here, Greg Levin, Laura Lee Johnson and ShaAvhree Buckman. Thank you.

(Applause)

Panel

Moderator: Virginia Recta, Statistical Reviewer, Office of New Animal Drug Evaluation, Center for Veterinary Medicine, FDA

DR. RECTA: Good morning. I got 10 messages that say, speak right into the microphone because that helps all the virtual attendees hear us better.

My name is Virginia Recta. I am a statistical reviewer in the Office of New Animal Drug Evaluation of CVM. I would like to thank Dr. Troutman and our speakers for starting this session off. Now we get to the panel discussion portion where we would ask the members of our panel to provide input on the three sets of questions that we have.

(Pause)

DR. RECTA: Our panel members are Dr. John Scott

from CBER, FDA's CBER. Dr. Dorothy Brown from Elanco Animal Health, Ms. Margie Bell from Animal Clinical Investigations and our two speakers, Dr. Chakravarty and Dr. Temple. So we will move on to the first set of questions, which are to do with what might be the applications that come to mind when we are thinking about adaptive designs.

We can start from that end of the table, Dr. Scott. So we have 45 minutes remaining with 5 panelists and 3 sets of questions. That is about 2 3 minutes per set of questions per panelist. I will start waving my hand if you get on to the 3 minutes. Dr. Scott.

DR. SCOTT: I will try to keep it brief. And I would just like to second what everybody else is saying, that it is a pleasure to be here. I would also like to second what Dr. Temple and maybe Dr. Chakravarty said, that I know little to nothing about animal investigations and can only guess.

But I can try to address this question insofar as it applies to human drugs and biologics, some of the conclusions we've come to and hopefully some of it is applicable to animal investigations as well.

So in terms of the question -- so how do these questions apply to animal drugs? Thank you so much. When we developed the recent draft guidance for adaptive designs for drugs and biologics, there are a lot of details in it, as

Dr. Temple said. It is about 25 pages.

But we tried to highlight what we considered to be sort of four key principles that every adaptive design should follow. And I think it is not just adaptive designs. I think it applies to all trial designs, and I believe it also applies to animal investigations as well as human trials.

So those four principles were first of all, that the trial should control the chance of coming to erroneous conclusions. Erroneous conclusions including Type 1 and Type 2 errors, false positives, false negatives, and also misleading information about benefit and risk tradeoffs.

The second principle was that the trial should provide reliable estimates of treatment effects, and this is something that especially in the adaptive design space we felt had been sort of under appreciated in the past, that sometimes you can use adaptive techniques to try to speed efficiency to get to a yes/no answer faster but part of the cost of that is more uncertainty about the quantitative estimate, about what the treatment effect actually is.

Another principle is that these designs should be prospectively planned to the extent possible, and that there should be detailed prespecification. We used the phrase complete prespecification in the draft guidance. I know you all are entering into a guidance development process. I can

tell you that industry was very concerned about the phrase complete prespecification. So that is something we are taking on board as we move into the final guidance.

We also talked a lot about maintaining trial integrity and ensuring that the conduct of the trial is not affected by adaptations or other complexities of the design in a way that it shouldn't be, certainly adaptation by nature changes the conduct of the trial but there are certain side effects or inadvertent consequences that you can run into.

So again all of those, I think, apply to any trial. In terms of some of the features that could be used, again I don't know what is currently used in animal trials. I think that it's widely acknowledged that group sequential techniques are usable and useful in a wide variety of situations. That in particular would include early stopping of trials for futility, when it's clear that the trial will not meet its objective, or early stopping for effectiveness or efficacy when it is clear that the trial, the investigational agent, has a very large effect.

I think that what I have heard is that CVM oversees trials that share something in common with a lot of what we see at CBER, which is that a lot of the trials are very small. And in a small trial, the group sequential techniques are arguably less useful. There is less information to adapt on, and you might need sort of the

entire trial database to get enough information about safety, about risk and other parameters.

What might be more attractive is sample size re-estimation techniques in that setting. Bob talked about what we sometimes call blinded sample size re-estimation, which is sort of free in the sense that it has no impact on the statistical operating characteristics of the trial.

This would be where, for instance, you reassess your impression of what the control rate is by looking at pooled data. And you do that with assumptions about the treatment effect.

There is also unblinded sample size re-estimation, which shares a lot in common with group sequential techniques. Here you take a look somewhere in the middle of the trial, see what the current estimate of the treatment effect is and revise your sample size -- usually make it larger if you overestimated what the treatment effect was at the design stage.

Another thing that might be attractive to think about are studies that combine dose selection and effect confirmation in a single trial. These are sometimes called seamless Phase 2/3 trials but there are a lot of different ways of doing this.

You sort of look at a trial as a multiple stage process, where maybe in the first stage you are investigating

multiple doses. In the second stage, once you have chosen one, you narrow down and try to get a confirmatory answer. Does this really have the effect it is supposed to have?

Another thing, and this is where I am going to go way out of my depth but I assume that in animal investigations there are a lot of interspecies issues where you have to do investigations in multiple species.

What I also assume is the case, is that a drug that is highly potent in one species might be likely to have potency in another -- maybe. Anyway, let me just cut to the chase. In situations where you have large heterogeneity, but some reason to believe that there are some commonalities in effect across those heterogenous groups, there are techniques that can be used like shrinkage estimation, where you borrow information across these different components or investigations.

I am getting a time signal from Jean so I will stop.

DR. RECTA: Thank you. Dr. Brown, please.

DR. BROWN: Thank you. So I am going to bring a little bit of the academic and industry perspective in. That is my history from the last 25 years. And so the opinions I am giving are based on that broad history and not necessarily just my time at Elanco.

So we definitely can include when we think of

adding an adapt revise loop to our traditional linear design, conduct, analyze. We can absolutely do that I think in a lot of the studies that we think about in animal health.

When we talk about which adaptations could be useful, so I will use my chronic pain background and think about those studies where we are really trying to minimize the big placebo effects that we see, for example. And so the adaptation for primary endpoint selection can be really valuable.

So for example, when we think of owner-outcome assessment instruments, there are multiple validated instruments out there, and any one of them could potentially be valuable as a primary endpoint of, for example, a canine osteoarthritis study.

But how any one of those instruments is going to work depends very much on what particular animals are going to be involved in that study, the characteristics of the sites and the personnel that may be changing sites at those different areas.

Geography, seasonality, all of these things can affect these outcome assessment instruments and the ability to take an interim look at your data and see which one is actually one that is going to be most appropriate for what is being accrued your study could be really, really, really valuable.

When we talk about what some of the limitations are, we talk about again a lot of the statistical aspects but there are big logistical aspects too. So for example, when we are thinking about owner consent and owner information forms, if you are in a change of study and change, make adaptations, mid-study, you will have to have a whole slew of owner consent forms that are approved and ready to go depending on which adaptation comes out the other end.

And then you have to make sure the correct consent form is actually being used at the correct part of the study so there is just complexity and detail in there that we need to think about.

When you think about drug availability, if you think about drug availability, if you get -- if you are changing, if you are dropping arms, if you are adding arms, if you are changing allocations to arms, making sure you can predict and have appropriate availability of the drug to the sites is a big deal.

And then as was mentioned, how you control access to your interim analysis is crucially important because it is so easy for subtle biases to get into the implementation of the study that can then affect the integrity of the trial.

When I think about where to the question, kind of that final question around where can these designs be applied, they can be applied early, early dose escalation

studies, all the way through confirmatory studies for sure.

There are going to be some studies and they may be based on safety or sample size in general, but when we think of studies where outcome assessment goes over a prolonged period of time, so where the endpoint is perhaps survival or maybe disease modification, if most of our animals are going to be accrued in the time that it takes to start seeing those endpoints, then adaptation is really not going to be valuable in those specific study designs.

DR. RECTA: Thank you. Ms. Bell.

MS. BELL: Hello. So I am going to speak from more of a statistical perspective. So reading through the human guidance, I kind of thought adaptive designs could be applied lots of different ways to animal health, which is really exciting.

I've been involved in sample size reassessments for animal health studies as well as futility analyses, and it is very helpful as far as the sample size reassessment if we see an effect and we need to increase that sample size, you know, that is a good thing.

But if we are not seeing any effect at all, it saves animals from being treated with a therapy that perhaps would not work. So as far as challenges, controlling the Type 1 error rate is a very big statistical challenge but the important thing to remember though is that the study design

needs to include the appropriate statistical methods to address the adaptations that are included in your design.

And there are approaches: the O'Brien-Fleming, Lan-DeMets, Pocock -- all of these can be used to help address the adaptations in your statistical model.

Another challenge is estimating reliable treatment effect estimates. Again these might contain some bias due to your adaptations so again if your model is including the adaptation, then the estimates will be adjusted and perhaps eliminate some of the bias.

As Dr. Brown mentioned, knowing the results of an interim analysis, that is a really large challenge. If we do a sample size reassessment and we decide that we need to increase the sample size, your sites and your investigators are going to know that we have decided to increase, and so this may be a potential for bias.

And to what type of studies for animal drugs would these study designs, I like the enrichment adaptation so if we had a treatment that maybe we think will work well in larger dogs and smaller dogs, then we could do an interim analysis and decide is it working better in the larger dogs or the smaller dogs? If it seems to do well in both, then we just continue, but if the larger dogs see a better response, then we would just change our inclusion criteria and include the larger dogs.

DR. RECTA: Thank you. Dr. Chakravarty?

DR. CHAKRAVARTY: So many of the things that I was planning to touch upon have already been discussed. Many times in human drugs, we have very limited sample sizes available, particularly in rare diseases or specific, you know, genotypes that we are trying to target.

So that parallels quite a bit into the potential sample size issue you may see in animal drugs as well. Just like others have mentioned, I have very limited background in animal drugs. I did do a detail in CVM about 10 years ago, so I draw upon that limited experience a little bit for my discussion.

So in thinking about what potential adaptations we might think about, sample size is not the only thing that we think of when we are planning to do adaptations. It can be the endpoints, as you mentioned, the population and things like that.

So in CDER there are some adaptations where, for example, a sponsor may use interim to perform sample size re-estimation as you mentioned and avoid the futility or inadequately powered study. On the other hand, a group sequential with event-driven interim may be used to reduce the expected sample size and the duration of the study.

It may include multiple looks that will allow for dropping an ineffective arm, thereby reducing the exposure of

animals. A potential challenge is controlling the probability of erroneous conclusions as you mentioned.

For example, if a group sequential method that can be employed to control the Type 1 error -- you know, we have used O'Brien-Fleming, Pocock, Lans-DeMets, depending on what the nature of the stopping should be. You want the trial to continue unless there is a resounding large effect. You may allocate smaller stopping probabilities in the beginning, and if you want to be equally spaced, then you are going to use others.

So depending on the situation, depending on the population and the disease that is being -- as mentioned, I also wanted to discuss the integrity of the study. About two years ago we had a public workshop on this topic, the entire day on this topic. And the reason is if a drug is approved based on an interim look, now the drug is available to everyone.

And it is difficult to keep the arm that is not on the drug, and there is some dissemination that is obvious so how do you make sure the rest of the trial is still interpretable? So that is a very big issue.

And I think CIDs can help in situations where there is a limited sample size. Also when, for example, we often use this in situations where you know about the adult population and you want to draw a parallel to the pediatrics

studies where there is not enough information. You are formally borrowing information from the adult study to the pediatric and so on.

So there are multiple ways in which it can be used, I think.

DR. RECTA: Thank you. And finally Dr. Temple.

DR. TEMPLE: I don't have much to add. I just want to make one note of something. That some of the methodology that is being talked about now involved borrowing from past experience, and that means believing it, and I'm highly skeptical of all of those things. I believe people will select the information they want us to borrow and believe.

I will be relieved of that when someone comes up with a Bayesian analysis based on adverse prior. That will resolve all my concerns. We will never see such a thing. It will never happen because why would anybody want to do that? They will try to ignore that.

But a lot of the things we are talking about involve a certain amount of belief, knowledge, that they've looked at everything, and how do you know that, and so on.

Even the one Aloka mentioned, which I think is an interesting use, that is you do a trial, it is a small population, so your control group, you shrink your control group by making use of past historical experience.

I have not seen anybody explain what to do when two experiences are somewhat different. Does that mean you throw them out, use them less or what do you do? Anyway all of those things have to be resolved before we know what to do with these things and the desire to use past experience is perfectly reasonable and plausible and sensible but the opportunity for shenanigans seems very large.

DR. RECTA: Thank you very much. In the interest of time, I think that Question 3 is probably more helpful to get our panel thoughts on. And we can go back to Question 2, which is more of a definition question. And if you have any input on Question 2 we can always get into the docket but in the interest of time, I think we can skip to this.

So this is a question on how might we facilitate the development and use of these novel investigational designs. Dr. Chakravarty has talked about collaborating with industry to design human studies. And how might this look on the animal drug development side?

So for this -- let me start, if I could, with Dr. Temple and then we will go the other way.

DR. TEMPLE: You are saying Number 3?

DR. RECTA: Oh, I'm sorry. Yes, Number 3. The set. We call them Question Number 3 but question set Number 3. The set. So all of those. Questions Number 3 but I think mainly the first and second bullet points are really

interesting to us.

DR. TEMPLE: Again my main problem with a lot of the issues related to complex innovative designs has to do with incorporating assumptions.

And I am not sure -- I think people need to sit down and think about how they will provide assurance that the assumptions are balanced, that they include all information, they are not selective, and they can therefore be considered reasonable.

For example, the question posed in here is leveraging external controls needs to be an understanding of potential comparability with concurrent controls. Okay, we say that every time we see someone propose it. I have not seen a suggestion of what to do. Mine would be, if the historical control is worse than the concurrent control, you throw it out, it is going to give you a false positive. So just toss it but I don't have a specified standard for what constitutes close enough. And someone needs to figure that out.

Or if it is very different, you downweight it, but even downweighting it, that means the concurrent control is being diminished in its relevance and yet it's the most obviously appropriate control.

So I think those things all have to be done with examples. That's probably my favorite use of potential

Bayesian analysis, that is to use a piece of the historical control along with the concurrent control but I have not seen a close analysis of what to do if they're different. And if they're different, they can either give you a false positive or a false negative. Somebody has got to come to grips with that.

And I haven't seen any discussion of those things, and I think it is really needed.

DR. RECTA: Okay, thank you.

DR. CHAKRAVARTY: So I will talk a little bit more on the partnerships. The CID pilot program is a prime example of using it in a very public and transparent form because you are sharing all the items that are in the disclosure element.

And I believe that, you know, if we can -- and I mentioned this in my talk as well, if you can see what worked before then clearly it's something that you can expand upon.

Again if it's something that you have very high potential for success, everyone was rooting for it, and then you see that it wasn't very successful, that also gives us a learning experience, this is reason why it didn't.

So that kind of partnership, especially in noncompetitive spaces, consortia or working in a professional working group. For example, for the statisticians, the American Statistical Association has undertaken certain

working groups. Those kinds of partnerships I believe will help quite a bit.

Now to the methodology, in certain situations, Dr. Temple mentioned about leveraging external controls. Clearly it has to be dynamically discussed because if it's a skeptical prior where you are going in thinking that it will not, then the level of borrowing will be very different.

And many times we come to it from a status quo. It may be a noninformative prior that you are coming into so it depends on the therapeutic needs, the patient population, all of that.

DR. RECTA: Thank you.

MS. BELL: So I was just going to skip down to what methods are needed such as the use of simulations and modeling to facilitate the designs.

Simulations are very useful. I've written programs that generate simulations, and you can test different hypotheses to estimate your sample size, see what will happen with your Type 1 error rate. You can also, you know, calculate things to -- the treatment effect bias, confidence intervals, just your variance that you might see with the proportions.

So the simulations are very useful and you just have to be sure to include your statistical model. And the statistical model needs to include the adaptation. Otherwise

you are not really going to find out any information that will be useful.

DR. RECTA: Thank you.

DR. BROWN: So I think when we are talking about partnerships we have to come from the space where we realize these adaptive designs have been around for 25 years or more. And other than again the group sequential designs, they are not really -- they haven't become a mainstay certainly in human and obviously in veterinary medicine as well.

And so the question is why is that, and the statistical literature is full of it, but when you come to the investigators and the clinical side, I think there is definitely either a lack of expertise or experience or clarity from the investigators' standpoint, the clinical standpoint about when these designs are applicable, what can and cannot be accomplished with these designs. What the practical implications of the designs are, some of what we've talked about here. And then how they are going to be interpreted and reported.

And I think very importantly there is lot of concern by investigators about health funding agencies are going to view these designs, and whether they are going to be put at a disadvantage compared to some conventional design. And then of course what the regulatory bodies are going to think about them.

So I think if we really want adaptive designs to contribute to our goals of delivering safe and effective therapeutics for the many, many unmet needs in veterinary medicine, you have to have kind of an all-hands-on-deck collaborative call across academia and industry and government agencies, the FDA. And you have to think about how you work within the constraints of the systems that we have.

So for example, in academia there are resources and allocations to doing basic and applied research and study design. There is very little knowledge about how to get a drug to market. And then the opposite is true of course that on the animal health side, there is an enormous amount of resources and knowledge about getting a drug to market.

But there is really usually very little resources allocated within the industry to doing the research that is needed on study design. So you really have to think about what are the collaborative joint appointments -- post-doctoral fellowships, internships -- that you can do across these different organizations in order to actually move forward with the research.

I think also we need to think about forums, as we've talked about. The public forums that we can have, collaborative forums where you have organizers representing all of those different groups to talk about the current state

of knowledge in these groups as well as lessons learned is really important.

So to get investigators to feel competent and confident to apply these designs, they need to understand what designs have been applied in the past and look at a lessons learned. What has worked well, what has not worked well. What could have been done differently?

And when we are talking about these novel designs, we have got to get them into the literature and we've got to get them there in a way that we can find them. So there is no indexing right now on adaptive designs, and we need to put adaptive design or adaptive trial in the title or in the keywords so that we can get the information back out because even if it is out there, it is ridiculously hard to find that.

So that all hands on deck includes reviewers of journals, editors of journals, and we have these forums that we put together now. I know in the pain space and I am sure in others. We have forums where they are organized by these members of these different industry, government and academia.

And that certainly can be done with the focus being on adaptive design and what that could look like for veterinary medicine.

DR. RECTA: Thank you. That's very helpful. Dr. Scott.

DR. SCOTT: So I agree with all of that. I think having multidisciplinary collaborations and outreach is very important. Some of the onus is on statisticians to do outreach on how these things work. But it's also important to remember that adaptive designs, these other complex designs, aren't free in a literal, financial sense.

These things require resources, they require planning and infrastructure. They are not necessarily the best choice in every situation. And you have to work with your collaborators to identify what's going to be the best design for the particular need.

We have had on a methodological level very productive working groups with industry and academics through the Drug Information Association or through the American Statistical Association on topics including adaptive design, Bayesian stuff, safety analysis. That is what we call it. Just technical terms, Bayesian stuff. It's all the stuff Bob likes.

And those interactions have been really good and I think useful for the statisticians from all sides of the aisle. But I think also involving the actual scientists and the veterinarian investigators and the clinical investigators in that process is extremely important.

In terms of journals and such, I want to mention some of you may be familiar with the consort guidelines for

reporting clinical trials in the literature. I don't know if those are used in veterinary literature. There is soon to be published an extension of the consort guidelines specifically for adaptive design, which hopefully will first of all make sure that they are reported well. But also may provide a framework for journal editors to understand how to talk about these things.

DR. RECTA: All right, thank you. We have time to go back to question, set of questions, the second set of questions. However, there may not be enough time for everyone to provide all their thoughts.

So what we are going to do is if you have specific comments on this, if you could add them to the docket, which will be open until August 17th. And we thank our panel. We appreciate your input really and for your presence here today. We know your time is very valuable but we will keep you for a few minutes more.

We have time now for public comments. My understanding is we have one registered speaker. If you could -- where is the microphone? If you could stand up at the microphone and state your name and affiliation.

Anne M. Traas, DVM, MS, DACT

Boehringer Ingelheim Animal Health

DR. TRAAS: My name is Anne Traas, and I am from Boehringer Ingelheim Animal Health, speaking on behalf of AHI. As animal drugs target increasingly complex diseases, it is imperative to explore new methods to evaluate efficacy in these diseases.

Regulatory agencies for human pharmaceuticals now widely accept advanced clinical trial designs. Some of these adaptive and alternative designs could translate to the animal health arena.

Adaptive designs allow for prospectively planned modifications to one or more aspects of the design based on accumulating data from subjects while maintaining integrity of the trial. These modifications may affect sample size, patient population, treatment arm selection, allocation to treatments and endpoint selection.

Potential advantages include ethical considerations such as reducing exposure to placebo and agility in diseases where less information is available.

Most importantly, adaptive designs have the ability to achieve the same outcome as traditional designs with fewer animals and shorter development times across a series of trials.

While the simplest adaptation, prospectively

planned sample size re-estimation, has been successfully applied in animal health studies and accepted by CVM, the benefits of more complex designs have yet to be fully realized in animal health where the number of animals studied tends to be relatively small compared to human health.

An example of an adaptive design which would seem to have ready application in animal health is the seamless efficacy trial. In this design, dose selection and pivotal efficacy evaluation are combined into a single study.

Other outcomes explored in a typical pilot study like safety may also be the focus of the first phase. Additionally designs incorporated an adaptive endpoint selection may also have an application.

While less is understood about the designs of this type, adaptive endpoint selection allows modification to the choice of primary endpoint based on comparative interim results where more than one endpoint is clinically relevant.

Examples of other novel and adaptive designs which might have a place in animal drug development include Bayesian designs, incorporating data from other sources such as pilot studies, foreign data or publications. Other designs such as adaptive dose finding methods for oncology, complex designs for mitigation of a high placebo effect, designs evaluating the effect of withdrawal of treatment and/or need for rescue. And designs incorporating biomarker

information could also be very beneficial.

Applying adaptive and other novel designs in animal drug development presents a few challenges and raises some associated questions. Perhaps most notable of these is the requirement for additional resources to conduct an adaptive design. Several discussions with CVM may be required before agreeing on a design potentially presenting timeline constraints for both protocol development and review.

For this reasons, we propose three important questions for consideration. First, how much data from pilot studies and other sources would need to be submitted to support the protocol?

Second, will new processes be needed to facilitate review of this data? Completely independent data safety monitoring boards and statisticians available to conduct interim analyses are standard in the human pharmaceutical industry but may not be available in the animal health space.

Third, what would be the expectations for validation of any software utilized for designs requiring intensive computer simulations to determine operating characteristics? Might CVM access to the software become a barrier to review?

Selection of appropriate adaptive modification

rules for animal health presents a particular challenge in veterinary drug development because of the need to balance the potential increased efficiency of adaptive designs with establishing adequate safety databases.

Would a new approval pathway where drugs are approved as efficacious with additional safety data collected post-approval be worthy of consideration?

Implementing adaptive designs may also have label implications. What effect would selecting an alternative endpoint or dropping a primary endpoint or other adaptive modifications have on label language?

In conclusion, many adaptive and novel designs employed in human drug development can be appropriately applied in animal health studies. Clear guidelines like the FDA draft guidance for Adaptive Design for Clinical Trials of Drugs and Biologics created specifically for animal drugs could facilitate adoption of these innovative designs.

Thank you for the opportunity to comment today. AHI looks forward to collaborating with CVM to consider scientifically valid, adaptive and other novel designs. Thank you.

(Applause)

DR. RECTA: So that concludes our first session. Thank you very much again to our panelists for their participation. We are going to go to a break until 10:45.

DR. ELLENBERG: At 10:45, we will continue the discussion for the next session.

DR. RECTA: Thank you.

(Whereupon, a brief recess was taken.)

Topic 2: Real World Evidence

Moderator: Emily Smith, Veterinary Medical Officer,

Division of Therapeutic Drugs for Food Animals, Center for Veterinary Medicine, FDA

DR. SMITH: Good morning. My name is Emily Smith, and I am a Veterinary Medical Officer in the Division of Therapeutic Drugs for Food Animals in the office of New Animal Drug Evaluation. And I will be introducing the topic of real world evidence and facilitating a panel discussion following.

So as was previously discussed in our first session, the purpose is to give you, our stakeholders, the opportunity to provide us with input and feedback so that we can draft a guidance that will help drug sponsors successfully incorporate real world evidence into clinical investigations.

To that end we have four sets of questions to guide the discussion; however, we welcome any input that you may have. And if you do not have the opportunity to speak today, we encourage you to submit the information to the docket.

So before we start our discussion, we need to

define a few terms.

(Slide)

So for human drugs and biologics, the law defines real world evidence as data regarding the usage or potential benefits or risks of a drug derived from sources other than traditional clinical trials.

In addition, within FDA's Real World Evidence program, the agency has further clarified the important distinction between real world evidence and real world data. Namely that the real world evidence is derived from the analysis of real world data, which comes from a variety of sources.

And Congress has now given CVM the opportunity to actively encourage the use of real world data generated in the course of the practice of veterinary medicine to generate real world evidence, which could be incorporated into clinical studies and our regulatory decision-making.

So as we seek to effectively incorporate this evidence, we would like to get feedback on a few priority questions.

(Slide)

First, what sources of real world data are best suited to generate real world evidence for animal drugs? And keeping in mind how real world evidence has been defined for human drugs and biologics, how should we define real world

evidence for making regulatory decisions for animal drugs?

(Slide)

Secondly, what challenges exist for the use of real world evidence for animal drug approvals? And what are the possible solutions to these challenges to enable us to more readily make use of real world data and real world evidence?

(Slide)

Third, in what context might real world data and real world evidence be used to generate clinical evidence for regulatory decision-making for animal drugs? And by context we mean potentially regulatory context such as new animal drug approval, a supplemental indication for an approved drug or even a conditional approval. Or potentially clinical context such as certain drugs or drug classes.

(Slide)

And finally what factors should we consider when evaluating real world evidence for animal drugs? What do we need to consider when evaluating the real world data and methods used to generate this real world evidence?

(Slide)

Before I turn this over to our speakers, we wanted to highlight the work that is being done across the agency on this topic. For human drugs and biologics, the 21st Century CURES Act required FDA to establish a framework for

implementing a program to evaluate the potential use of real world evidence to help support approval of a new indication for an approved drug or to support or satisfy post-approval study requirements.

Because of this framework that is being established, there have been a lot of great resources published by FDA in response. And we may be able to leverage some of this work and jump-start our progress in this area. But at the same time, the guidance and processes that we develop for new animal drugs need to be tailored to the types of real world data available for drugs for veterinary use and the types of real world evidence will also need to fit the regulatory needs of new animal drugs.

(Slide)

And finally we wanted to share a couple of examples of where CVM has already started using real world data and real world evidence in our regulatory decision-making.

So for example, sponsors have provided CVM with real world data as part of the justification for selecting their drug's dosage or to justify elements of clinical study design.

(Slide)

And we also have one example of where real world evidence was included as part of a study that provided

substantial evidence of effectiveness for a new animal drug approval.

Included as one of 21 studies in a systematic review and meta-analysis, we had one study that provided real world data from clinical records of practices specializing in dairy cow reproduction. And these records were compiled in a retrospective study.

(Slide)

So we are excited and looking forward to expanding the use of real world data to generate real world evidence for animal drug approvals, and have two speakers that we are going to hear from today who will also participate in a panel discussion following their presentations.

Our first speaker is Dr. Elizabeth Lund, who is president of the LLC Data Dogs. And our second speaker is Dr. Laura Hungerford, who is head of the Department of Population Health Sciences at the Virginia Maryland College of Veterinary Medicine, Virginia Tech campus.

So I will invite Dr. Lund to come and give her presentation.

Invited Speaker No. 1

Elizabeth Lund, DVM, MPH, Ph.D.

President, DataDogs, LLC

DR. LUND: Thanks, Emily. I am really thrilled to be here. It is over 25 years that I have been working

with real world data. Can everybody hear me okay? Okay.

And so when I was doing my Ph.D. 25 years ago in the early '90s, it was funded by the Pew Foundation. And Pew was looking for options for experimental research using live animals.

And so it was over 25 years ago that again we were looking at this idea for animal welfare purposes. But I think now it is definitely an idea whose time has come, and for a lot of other reasons as well.

(Slide)

So just to give a framework for what Emily has already given our background on, what I am going to address when I go through on the companion animal side, and just to let you know, pretty much everything I am going to be talking about is dogs and cats, so small companion animals.

Although there are definitely examples, say, for horses, of some population-based studies. My experience and my comments really are going to be specific to dogs and cats, so small companion animals.

So really the goals and why we want to evaluate the potential for using real world evidence driven by real world data -- I can't say those very quickly -- are to accelerate and innovate medical product development. Create efficiencies, especially for the R&D process. Efficiencies not just in research but in use of animals in the process for

approving drugs.

Support approvals of new indications for drug use, and then also post-approval studies, post-surveillance, post-marketing surveillance.

(Slide)

And I think it is really important -- some of you are probably aware of these trends but just to set some context. So over the last couple of decades there have been some really important changes in the veterinary services profession. So where largely, say, 30 years ago veterinarians went into private practice, and all practices were basically small-business owners, there has been increasing acquisition and consolidation by corporate players in the veterinary services market.

So starting in the late '80s, early '90s with VetSmart, Banfield, now Mars PetCare, there are multiple large practice networks. Although there is not a real specific number of how many practices are out there and how many of those are corporate owned, there are probably about 30,000 practices, and anywhere from 10 to 15 percent of those practices are corporate practices.

And this trend will continue. So for a lot of the reasons we are talking about the efficiencies that can be gained by using real world data and real world evidence. There are efficiencies from a business perspective in terms

of buying and purchasing, when you consolidate and create practice networks. There are at least two practice networks with over 1,000 practices in them. And this trend is likely to continue for the next 5 to 10 years.

Nobody expects that there will no longer be private practitioners in place but the trend right now -- there is a lot of venture capital and a lot of practices are being consolidated. And with that trend, not all practice networks but a lot of the large practice networks have a single -- this is specific to what we are going to be talking about -- electronic health records. They have a single proprietary electronic record system.

So all practices, say, in a over 1,000-practice network are operating in the same practice management system, the same electronic record system. So you can imagine from a standardized process perspective and a data capture perspective, there are great efficiencies and potential there.

That being said, within those system, unlike in human medicine, there is not a single standardized system for nomenclature. Basically nomenclature is just coding or -- it is a common language for describing what happens in a medical encounter. So diagnostic nomenclature. ICD is a common standard used on the human. There are standards developed for veterinary medicine but they have not yet been engaged on

a wide level across practice networks.

The other thing, and I will continue to talk about this, especially when I talk about the opportunities and our challenges, is rarely -- these systems are used to provide veterinary care. So what's important is the pet in front of the veterinarian and the veterinary team taking care of that pet.

And so those systems -- the data goes in and the data is coming out or supporting clinical care. It is not an R&D data capture system. They are not asking research hypotheses of these systems.

So it's really important, again, to understand why the system is in place, how it's used and how people interact with that system.

And then the third thing that I think totally makes sense when you consider how these systems are used is that outcomes are not consistently captured in these practice management systems, the electronic health record systems.

You get a patient who comes in with a fever, fever of unknown origin. Maybe it's a UTI. You don't know. But you give that cat or dog antibiotics. Well, that pet doesn't come back in two weeks necessarily even if there is a response to therapy and the pet is better. It is likely not to come back to the practice if it has resolved and it has gotten better.

So from R&D and the product development perspective, understanding that limitation. I think there are, and I will talk about this more, I think there are some great ways we can create hybrid designs so we can use, for observational research, electronic records and then create other sort of outcome assessment into those studies.

(Slide)

So really what I did is I just took sort of from the guidance on the human side and what Emily, as we worked to put this together, I just sort of took what we know on the human side that has been done, and there is potential, and has been used. Where we have the most experience, and where I think the most potential, especially short-term, is.

So it's just a really quick and easy schematic. Just dogs. So the more dogs the better. So there is a lot, there has been a lot of research done with electronic health records, population research, observational research, epidemiologic research -- whatever you want to call it -- with electronic health records in veterinary medicine.

Medical claims and billing is a little bit more complicated. Insurance in the United States, you know, 3 percent at the most of all pets are insured. Probably about half the population of pets in Sweden are insured. And so there has been some really good population research using claims or insurance databases in Sweden. And I think there

is a lot of potential.

Even if you have a smaller, say, population to which you are getting the data, if you can, in a valid way, say that population is like the greater population even if they are uninsured, I think there is still value in that evidence and in that data.

I think where we are probably more limited, but I think it's an important part of our journey in this area, is with product and disease registries. And again keep in mind those are just -- usually just what epidemiologists call numerator data.

So we really don't know the population at risk. We know those, say, for adverse events who were affected or for registries, who has the disease. So coming up with a control population is more complex and super-important.

So again just comparing contrasting again on the human side with veterinary medicine, observational studies. We have a really fair amount of experience in this area now. And there is also a group -- and I have them on a slide later on -- a group called Vet Compass in the UK. And they are actually a network of over 1,000 private practices, and they pull data out of the back end of a system. They're also going to Australia.

And they use -- they don't have standardized nomenclature either but they have a lot of grad students who

do some machine learning and coding of outcomes and diagnoses on the back end. And they've published quite a bit, Vet Compass.

And I think I mentioned hybrid designs around outcome assessments. So I think there is great potential. I only gave them one dog because I don't know if we have much, if any, examples of that so far but I think there is great potential.

And then and from the data perspective, claims data, I mentioned limited insurance databases but electronic health record and then lab data because really there are two big labs, veterinary labs in the United States.

And that data again, with those networks, is standardized and is a big potential. Pharmacy data, I don't have a lot of experience or know how that has been used a lot.

(Slide)

So I wanted to give you a couple of examples, one of comparative effectiveness. And this was a study of canine heartworm medication called ProHeart 6. And it was compared to Ivermectin. ProHeart 6 is an injectable. Ivermectin is oral, and then there was a control group.

And this is from a practice -- there are about 500 hospitals, 12 million records, in each of the arms of the trial about a quarter million dogs. It was a retrospective

cohort so they went back in time in the electronic health records of a general practice, primary care practice. And then they looked over time for the effectiveness of ivermectin compared to ProHeart.

And what's really fascinating is that there are slight differences in effectiveness, 94 percent and 96 percent, but when you looked at the experimental research that supported efficacy for these two drugs, it was 100 percent. But those are experimental, very controlled, clinical situations.

And so what I loved about this was this was a real study, real world data, real word evidence. These were pets coming to see general practitioners. And this reflects that effectiveness, reflects sort of real world -- there is compliance. You can see the difference between ivermectin, which is oral -- more challenges to oral administration of a drug versus an IV preventative that was given by a veterinarian and lasted for six months.

So on the basis of this study -- and so this study was a response to voluntary withdrawal of ProHeart. I am sure a lot of you know the story. There was also a safety study done. The company also did -- made changes to the product, and based on a number of things it was reintroduced in the market in 2010 I believe, and I think ProHeart 12 just this month was approved by FDA for use in dogs.

So I think it was a great example of how you can use real world data, real world evidence in a very impactful way. Because compliance is so much better in an injectable drug, you are helping a lot more dogs be protected from heartworm disease.

(Slide)

The next study, again with this same general practice, primary care practice, millions of dogs and cats seen every year, this is a great example, although it didn't actually get instituted. It was a partnership with UC Davis. Phil Kass is an epidemiologist. And they created a novel algorithm for doing syndromic surveillance.

And imbedded in the records of this general practice for this dataset for this study there was -- these were for food-borne outbreaks in aflatoxin and then a salmonella. And the syndromes could be based on clinical signs, laboratory tests, biochemical tests.

And so with the imbedded alerts, and the investigators at UC Davis were blinded to these, the timing of them, they were following them, they created sort of 90-day rolling averages to detect peaks. Alerts were generated on the day, on the first day of both outbreaks.

So again it was manually conducted and then the next step was to go to an automated process, which without additional funding we didn't move forward. But it was a

great example of using -- again you have both numerators and denominators when you are following a real-live population of pets over time. So you don't -- in adverse event reporting, often all you have is the numerator, the pets that were affected, and you don't know the whole population from which those pets come.

(Slide)

So I have sort of touched on these things but what I really think -- in a way, it has always been obvious to me I think as an epidemiologist so that is my own admitted bias -- is that one of the greatest opportunities and advantages is when you are doing research in the population to which the results of that research are going to be applied, it is much more generalizable and valid.

You think back to the heartworm example. Well, in a very controlled, not-real environment, they were getting 100 percent effectiveness or efficacy of those products. But when you actually use those by veterinarians, real vet teams, real clients, real pets, especially with an oral product -- with an injectable your compliance is better -- with both of them the efficacy was not the same as it was in a controlled clinical environment.

I think there are just great sources of -- besides electronic health record data there is laboratory data, there are existing large data sets for pets, for small,

companion animals. So again, just going back to this efficiency of existing data, again understanding that none of that data was collected specifically for research but you kind of have to balance, you have to bring rigor, but you are balancing with reality.

And there are advantages then when you then apply those results to the population from which those results are generated.

We talked just briefly about the post-marketing surveillance study and syndromic surveillance. The power again of finding a whole population. You have the denominators. You know who the whole population at risk is.

You know, vomiting, diarrhea happens a lot. And when you have adverse events and only have a numerator of vomiting or diarrhea, well, you don't know -- a lot of pets get vomiting and diarrhea, especially young dogs, who eat everything.

So it gives you a context, it gives you a power of understanding that you don't have again when you just have numerators.

And I talked about a lower insured percent of insured pets compared to the human side. Basically everybody is insured. But one of the things that has always been fascinating to me about the lack of insurance on the pet side is that on the human side, often, you can imagine that

when you are coding or when you're trying to optimize revenue, it may influence how you use a coding system to code human diagnoses to capture -- for medical claims.

Because we have such a low percentage of dogs and cats that are insured, that is a bias that we really don't have to worry about. So I have always found that fascinating.

(Slide)

So our challenges, and nothing real comes without challenges, I've talked about standardized diagnostic nomenclature, and although one exists, there is a secretariat for SNOMED, which is a diagnostic nomenclature. So in human, on the human side, there is a veterinary secretariat and a team at Virginia Tech.

And they've created a subset or an extension of SNOMED for companion animal, general practice, specialty practice and equine. And the real challenge -- a lot of software practice management systems have imbedded those codes, that system into their software but there is not widespread use, and I will get to this, my last bullet, which is what is the value proposition for a veterinarian to consistently capture diagnostic codes in their records?

Although it would mean a lot for us as researchers and epidemiologists, what is the value proposition for them? I mentioned at the beginning two

medical outcomes, and I think they're inconsistently captured. It doesn't mean there can't be biomarkers, laboratory tests, things that are used. But I think that's a bit of rigor from a population research standpoint that I think we'd have to be really thoughtful about as we hopefully use more and more observational designs in this area.

Another big challenge but I think technically it's not as challenging maybe as it has been is interoperability. And all that means is practice management systems to be able to talk to each other.

So within a big practice network, can all those, a thousand hospitals, can they talk to each other? Can you go to a hospital anywhere in that network and have all your medical record data available?

We know just as consumers ourselves of human medicine, a lot of times our records -- we may see a specialist but our GP might not have the results. And that's also true on the veterinary side.

So I think ultimately that -- I think for moving technically to solutions around that but that challenge exists for veterinary medicine as it is human medicine.

And then I talked about the value proposition, and that's across many stakeholders but when you think about electronic health records, they are for the purpose of taking care of a pet.

And the time is always squeezed for any veterinarian in an exam room as to what data they put in and whatever they have to do to that data to get it in a management system is only -- the best value for them is how they're going to take care of that individual pet not how we are going to aggregate data across a population to analyze in a regression model. They don't care about that.

So I think we have to create -- what value is that research then for them? And ultimately that can motivate them.

(Slide)

So this is a little messy as a slide but the future is always a little messy. There are a lot of potential devices that we can capture data from. I have a slide up there with a little puppy with a wearable device and an activity monitor, accelerometer.

There is great potential in that data. It has not been validated yet so there is a lot of important work that has to be done to validate those activity monitors to specific outcomes. And they are probably very specific to certain disease. There are dashboards, there are pet owner apps that would be a huge source of data. Genetic data. I have a little icon there for Vet Compass, which I think they are doing some amazing things.

And then there is data across this whole what we

call the pet eco system. The groomer, the boarding facility. And again, technically, as our whole world gets more and more connected, whether we want it to be or not, I think a lot of these technical challenges will get solved.

Interoperability won't improve but I think it's really critical within agencies like FDA, academia and industry, we have to start building the capacity and the infrastructure to leverage this data.

It's a different skill set, it's a different paradigm, it's a different way of looking at the world. And again, maybe as an epidemiologist I have always thought differently about the world but I think there is a time, like I said. We really need to bridge sort of the rigor of what population methodology can bring with reality. And I think we're all winners in that.

And I think there were brave discussions in the first panel about partnerships, consortia, collaboratives. There are multiple stakeholders who can benefit from use of real world evidence and really the sky is limit.

(Slide)

I am going to leave you with one of my favorite quotes from Ram Dass. And I thank you for your attention.

(Applause)

DR. SMITH: So our next speaker is Dr. Laura Hungerford.

Invited Speaker No. 2

by Laura Hungerford, DVM, MPH, Ph.D., CPH, FNAP

Virginia-Maryland College of Veterinary Medicine

DR. HUNGERFORD: Hello. Thank you first for the invitation and the opportunity to be a part of this. I think it's a great opportunity to ask a question that is already dealing with things that are happening and to communicate about it.

I had the opportunity to be a senior advisor for science and policy for FDA until about three years ago. So I got this glimpse of the really amazing stuff that is going on inside of FDA and particularly within CVM that most people don't get to see.

And so one really exciting part about this meeting and about the guidances are that it really is going to bring more into the open what is going on, and the kinds of thoughtfulness and new ideas that only sponsors get to see and people that work at FDA. And so it will increase the visibility I think in a way that is critical to how we make better efforts to improve animal health.

(Slide)

So the fundamental, no matter what kind of evidence we are using anywhere in animal health, the fundamental important piece is the necessity to weigh evidence in order to make our decisions. And it doesn't

matter if evidence comes from laboratory studies, from randomized controlled trials or from other parts of real world data. They're all evidences that it is important to be rigorous and think about in our decision-making.

Now for epidemiologists in academia and other places, we can be a little more wild and free about how we make our comparisons and what we do. But fortunately for drug approval, the guidelines that are out there, the regulations, and the law for FDA, prescribe that it's important to make good decisions and look carefully at the evidence.

And sometimes they may be overprescribed, but it really is with that goal of making sure the comparisons are good.

Now when we look at real world data and real world evidence, there is no reason it can't fit into this framework because we should be rigorous in saying what can we really conclude. But the place that's important I think not to be caught is to come up with a guidance that prescribes specifically the approaches that need to be taken to answer these questions because we don't even know how these data will be able to be collected in the future but we do know how to think about making good evidence-based decisions.

(Slide)

So in the traditional way of looking at new

animal drugs as well as new human drugs, we deal with new chemical entities. And ultimately in weighing scientific evidence, the critical thing is to say what's going to happen not when we are doing studies to submit or reviewing studies, but what is going to happen in the real animal populations after this is approved?

And so the only way to really do that is to do experiments and to use experimental data to try to make that inference to another population that may be close or may be different. Some of the things that Dr. Temple talked about this morning are ways to better do these trials but they pick animals or people that are more and more homogenous and maybe more and more different than the populations in which they will eventually really be used.

So the opportunity here is with certain kinds of entities that are already out there, the drugs are already being used in animals and people. And most particularly these would be already unapproved animal drugs that are used. It may be coming up with new indications for drugs that are already out there, adding a class or an age or a type of species to a drug. Or drugs that are in the process of conditional approval.

Here we're not bound to ignore what is happening in the real world but we can have data from the real populations and not be stuck trying to infer to a population

we've never seen what is happening and we are trying to get a little glimpse of that.

So real world data and real world evidence are ideal in these situations because they already exist, and to put things into a traditional paradigm, we'd have to ignore some of the most valuable information out there.

So we can actually ask what is happening in the population? Of course the caveat, particularly as Dr. Lund was talking about, is we may not always be measuring what is happening in the real population so one of the challenges with real world data is to have things that are measured in a way that is reliable and that we can use in decision-making, which in the practice of medicine or in maintaining animal health in herds, is not always a top priority.

But I think it's becoming more and more the case that people want to have answers when they have records and so I think we are moving that way, and so it is good that this discussion is happening now.

(Slide)

Now although this public meeting is new, this idea of weighing real world evidence is not new at all. Within FDA there is a strong basis of guidances already from some of the other parts of the agency. So this puts CVM in a great position because they can look at this baseline of all the thousands of hours of work that other people have done on

their behalf and then pick the best pieces of it and modify it to work well.

They can also look at the things that are maybe not working so well and not have to go down that path but rise above it. So these are really powerful. In addition, there are partnerships that the animal side can be a part of that the human side is already doing. And you heard descriptions this morning of some of the pilot projects that are looking and preventing more external information on some of these new designs that are being used.

So that's a great opportunity to share what's going on in a more structured way because having been inside, as I said, some of the things that sponsors are planning, doing and working with FDA to do on the animal side are truly amazing and are really very efficient and effective in answering better questions to move toward animal health.

(Slide)

Now one of the problems I think that we can get into with real world evidence and real world data is that we're so used to doing randomized controlled trials that instead of asking how do we weigh the evidence to decide if a drug is safe, effective and is of high quality? We can start to say, well, how does the real world evidence match up with a randomized control trial that's kind of the best strategy that we've used in these more experimental methods?

But randomized-controlled trials, even if you think about what is the best kind of design, is not at the top of strength of designs. It's really those designs that are systematic reviews or meta-analyses that pull across multiple, multiple studies in different populations and include generally real world and experimental data that are the strongest.

And so I think while randomized-controlled trials have lots of strengths because of the randomization and the controls, which are very important, they also have their limitations. So just to remind you of proceeding cautiously with randomized-controlled trials, especially sometimes when we are trying to do them in animals when they're not very large. We know that there are a lot of limitations.

Some of the design enhancements talked about this morning make the populations more homogenous so that you can find the effects better but maybe make the humans or animals less generalizable.

So maybe we find a good result of the clinical trial but maybe it doesn't apply to the population we are going to use it in, in the end. I think we work as hard as epidemiologists and in regulatory agencies to try to make those two match up, but you can see on the human side more and more Phase IV trials that look at how does this really work?

I think Dr. Lund gave a great example of the trials of ProHeart and ivermectin, and then what happens in the real world, and does that match or it doesn't. In that one, it matched well. But in other cases, it may or may not.

For new chemical entities, there is really not a choice because you need something to infer what will happen in the population. But with things that are already out there, we can overcome some of these problems perhaps by relying more on real world data and including those kind of evidence for both effectiveness as well as safety.

(Slide)

One of the biggest concerns I think for looking at safety that we have the advantage of real world data to help overcome are the small sample sizes that we have in studies. So even if we have a study with very, very few problems or safety effects, if you think of the very small number of animals and the confidence we have about that and then multiply it out to the number of animals that it will be used in, we really don't have a lens in a small study for really knowing how safe it will be in the end.

And so real world data give us ways to look at these kinds of things.

(Slide)

Now if we are going to move away from using just randomized control trials or just experimental data in

animals, which you can see is kind of toward the bottom, it still doesn't move away at all from this ability to constantly remember we are weighing scientific evidence and we have to do that well.

And as you move into observational studies or other sources of data, it becomes more and more important that you really have well-designed hypothesis-based studies that recognize all the potential biases and problems that can be in the data that you're looking at.

There are a lot of publications on the human side that guide people through learning and thinking about biases. How in one kind of study, one thing will be a bias. In another population, the same kind thing that was a bias might become a strength.

So it really takes an individualized -- what is my hypothesis, what are the biases, and how do I work with epidemiologists, statisticians and clinicians and a whole group of others to balance those and come up with the best design to get at the question.

And the critical thing, often as epidemiologists, we may have a database and we go looking for what are interesting hypotheses to generate. Or we go fishing, which is not something that can be used in putting together evidence to look for the important outcomes of effectiveness in studies.

(Slide)

Now as I said, this is not something new. So here is an article from 1999 by Dr. Temple, who spoke this morning, actually looking at epidemiologic studies in drug development. I don't know if he is still here to say he has been thinking about this a long time but thinking about it well.

You've heard a couple of examples. There is the example of Folltropin that was approved, and if you look at the FOI, you can see the different kinds of studies that were incorporated in part of that. Commissioner Sharpless talked about the novel approaches for fish that Dr. Storey has been using. So there are a lot of these great ways -- this is already happening without being able to tell you until they work with the sponsors to talk about the specific information and follow up.

(Slide)

And then for safety, we did a systematic review that looked at potassium bromide and actually found that the data that were out there were much richer, much fuller and much more complete than what we would have found in a traditional target animal safety study that would be done with a limited number of animals.

So these things are already being done. It is just a matter of moving it to making it much more viewed.

And how do we do that? I think there are three ingredients that we need in order to successfully move this forward.

(Slide)

The first is recognition of the strengths and weaknesses of animal electronic health records, which Dr. Lund talked about a lot. These are becoming more and more widespread. But again they're not designed to do a clinical trial or to do an observational study for drug approval.

So there are limitations but I think thinking about what those are, what we can do with them and how we might be able to use them -- this is the perfect time for that.

Additionally I think as veterinarians and practitioners and academicians become more aware and these records become more widespread, those same questions of comparative effectiveness and what are the underlying factors that drive health and drive safety are going to be more and more approachable by people and practice as well.

So I think the databases may adapt themselves to allow these questions to be asked better.

On the food animal side, where we're fundamentally managing health and efficiency in populations, these databases may be more applicable because people are already trying to use them for decision-making.

And when you put them together, for example, with

feed lots that have specific treatment SOPs, they want to follow up, they want to know the costs, they want to know the effectiveness, I think we already have databases that are proprietary but that take us in this direction.

And there are more and more, with more distantly accessible all the time.

(Slide)

And so when we think about these kinds of records, being able to supplement them with a wide range of other kinds of sources of collection I think is one of the other huge advantages of real world data.

We know, for example, especially when we work on livestock, that even collecting the data on how a drug is working, we have to run them through chutes. We have to handle them in ways that probably introduce another effect into what's happening.

And so the ability to have wearables, facial recognition in cattle, monitors that talk about how they are moving around and are they well or not, swallowables -- all sorts of ways that we can measure real world data and put that together to get a much more complete picture.

And even to follow up, as Dr. Lund was saying, animals that -- maybe they don't come back in but maybe their collar sends us what happened with their temperature and their well-being and their movement or their pain levels

because of how they moved.

(Slide)

One of the big things though is to get these records to talk to each other. So ironically when we are talking about population records, we still treat the databases as pets instead of populations. We don't have them work together, be a greater whole and talk to each other.

So one of the things that's going to matter in the long run to get real inferential and generalizable ability is to have better connectivity between these data sources and be able to share better. Not just I have records in one lot and someone else who is a totally different, noncompatible system but how does this work in different places across the country or across the world?

(Slide)

Another ingredient: We may have all this data, these data, but to turn them into evidence we need people who can work with the data and who do this and think about biases and ways of analysis as just what they do every day.

And so this brings engagement of the veterinary epidemiologist as being something important. And earlier, I think Dottie had mentioned that academicians and people doing drug research often don't talk to each other and don't share their knowledge and don't work together even though we are asking the same questions.

So there are a number of organizations but I think engaging this group, they are huge resources for that transition between real world data and real world evidence.

And they're aware of the dangers, they're aware of the strengths. They think about bias all the time. And in fact they think and talk about bias not only in their work but if you get a bunch of epidemiologists together over a beer, they are talking about data and data sources and coupling them and biases. So they think this way all the time.

So I think it's an untapped resource that can really help with the stringent study designs and help with how do we do this and make these into evidence in really creative ways. And also spell out the dangers. Where should we not ask a question? Where do we have a question and we need a totally different type of data? And then how creative can it be, especially when you look at the new group of graduate students and people coming up who thrive on monitoring things in very strange ways.

(Slide)

And then the last ingredient I think is CVM itself. So I told you, having been able to share in this environment -- the knowledge, the expertise, passion and experience there because usually when we communicate in science, it is publications, and that's not their mandate.

Their mandate is to approve drugs, look for safety, and that doesn't get shared outside except to sponsors.

And so an ability to have a better understanding of the great stuff that is going inside and to know what opportunities that pose I think is a critical part of this ability to make this happen and to engage in that way.

And actually they have lots of avenues for feedback, and they have lots of preliminary types of meetings and places to bring ideas and have discussions, as were talked about for the other parts of the agency this morning.

So that's a really important ingredient as well, and is probably the key to this whole thing but it's also the best-kept secret.

(Slide)

So in summary, I think it's really important as we go forward in this area, and in thinking about putting together a guidance, that it really focuses on the questions and the evidence and how you think about that rather than saying it must be this, it must be this, it must be that.

Because about the time that gets written, the new ways of collecting data, the new ways of integrating data, the new things we haven't even thought of will be coming out. So it needs to go back more to this: How do we weigh the evidence? How do we come up with a critical question and then what is the right group to put that together?

And I really liked this morning when Dr. Brown mentioned that the way to take advantage of all these new designs, and probably everything else we talk about today was an all hands on deck collaborative call.

So I think that really is the message for making a successful guidance. How do you have those discussions? How do you take the best new ideas and use them with this bar of seriously weighing the evidence to come to conclusions that we can put our faith in? So thank you.

(Applause)

DR. SMITH: Okay, so as our speakers have addressed the priority questions in their presentations, we are going to follow with a panel discussion with some additional questions that dive a little bit deeper into the topic.

Panel Discussion

DR. SMITH: So my first question for you both is what do you think will be the most viable sources of real world data to generate real world evidence for animal drugs?

DR. LUND: I think there are going to be multiple streams but I think the most potential that's been proven and demonstrated, and we should definitely with some sense of urgency continue to build on, is electronic health record data and laboratory data because I think by volume and -- although there is more work to be done around

standardization, I think we've got large repositories of that data but at the same time in parallel I think we need to work on the activity monitors, the app data.

All those things are going to be important. I think those are all additional parallel work streams to the electronic health record and lab data.

DR. HUNGERFORD: And I would agree. I think that's true in a general sense. I think particularly important though is to look at what is the key question we need to answer? What do we already know? And sometimes there is just one little piece that we still need to know.

And so maybe finding what would be the ideal source of those data. Do they exist someplace or how is the best way to capture that and put it together with everything else because I think often we ignore everything that's already out there.

And so doing an analysis first to say what do we know and what do we still need to know to have the right evidence. And then finding that evidence even if it's something very strange or measured in a weird way. As long as it's filling in the gap in the rest of the piece, I think it becomes critical that way.

And I don't think we know what those future ways of data collection could be. Often what we study I think are things that are measurable and we are satisfied with

measurable, maybe not as much as optimal.

And so maybe even in some ways -- I know on the human side, they are looking at patient-oriented outcomes and things like that, figuring out what is the best way to answer this question. Maybe it's something we've never measured before but maybe in the future there is a way to measure it.

DR. SMITH: Okay. Our next question for you is what factors should we, as FDA, take into account when evaluating a source of real world data?

DR. LUND: There are a number of points in this, and this is something I probably could talk ad nauseam about. I think it's so important to understand the context and so I talked about these proprietary electronic record systems. You need to understand the operational source or operational context for how that data is entered, the system that was developed by human beings for -- we talked about primarily clinical care.

You have to understand the human factors. What are they incentivized to enter? So if you do something, say, during a pet encounter that isn't going to capture revenue, well maybe it never makes it into the medical record even though it could be a critical component of that pet's health record.

And if you are getting paid, if there is a capitalization on how you are getting paid, you are going to

make sure you enter the things that again generate revenue.

Standardization of data capture, I have talked about that. From a data warehouse perspective, that's very critical too. What are the rules and the logic used when that data is captured into the system because I don't like the phrase garbage-in, garbage-out because we're all just humans trying to do the best we can but again thinking about how humans behave and why they behave in a certain way is a critical component to understanding this context.

And then understanding -- we talked about outcomes too. How those are managed, how those are measured, and that's my laundry list.

DR. HUNGERFORD: And I have just a little bit to add because I think Dr. Lund's expertise in this area, those are critical things to consider. The only things I'd say is sometimes we don't think about again what is the outcome we really need to know? And is it measurable, and how is it measured?

And I think now with thinking of real world evidence, it gives us an opportunity to do that, to say what is the best way -- what do we really, really want to see in these animals if the treatment works? And the other is, did we get the right animals?

I think there are a lot of concerns when we -- even if we have perfect electronic health records, are the

right animals captured in that system? Or are they convenient animals? I think those would be the only two but those criteria for deciding how good the data are, are critical that you described.

DR. SMITH: So in both of your presentations you touched on the concept of bias. So what do you think are the most important types of bias to consider with studies generating real world evidence, and how should we control for this bias?

DR. HUNGERFORD: So I think bias is very context specific. There are some great examples where when people are doing systematic reviews, they have checklists to go through and think about all the biases. So I think the biggest thing is to come up with -- I usually think about if I'm planning a study and my worst enemy is going to critique it, where are all the places that they can say, oh, that's wrong because you didn't do this.

And that helps me think about those biases that I might not have thought about and how to control those. And in general we think about biases in the way, you know, that we select the animals, selection bias, and that can be selecting the records after it happens.

And we think about how we measure things, information bias. What we measure on the animals. I think thinking about each component of that becomes really

important so that we can have kind of a laundry list to go through.

Because I think the biases that affect every study will be different because of the very things that Dr. Lund mentioned about who is in it? How they were collected and why?

And then of course there is the bias of -- and we talk about publication but it's really not that. It's are the data in the studies accessible? Can we find them or are we only finding the subset that show what someone wanted us to see? So how do you make sure that you have that complete things -- the best and the worst of the particular pieces of evidence.

DR. LUND: I would go back to my laundry list for evaluating sources of data because it's one of those answers to questions you hate to hear but it really depends and because it is complex. Really, the context is so important.

An example of this just from one of many is just how you make a diagnosis. And so if a disease on exam is able to be diagnosed, say, otitis. And you can put that in your system, well, it's there. If a diagnosis -- you have to wait for a lab result like a thyroid disease, hypothyroidism. If you don't get that result right in the exam, you're missing an opportunity to enter a piece of data.

Again that's just a simple example of the bias

around the prevalence of a disease in a population. So you almost have to understand the workflow and again the system. And it is so context-specific. It really, really depends.

DR. SMITH: So realizing that this area is going to continue to evolve but there is a current state within veterinary medicine. What study designs do you think at this point are best suited to the real world data that's available to us in animal drug development -- and should be the points of focus right now in a guidance?

DR. HUNGERFORD: So I think it depends on what the question is that you are asking. So I think for safety data, all bets are off. I think all data that are out there need to be looked at carefully.

So for example, in a safety analysis, a case report may be a higher level and better evidence than a small cohort study that really wasn't powered to detect very many adverse events.

So it's going to depend on putting together all the sources of data for safety, and inferring from other species. It is a much wider net without a real study design that's ideal.

I think on the study designs for effectiveness, traditionally cohort studies are the strongest among the observational but I think combined studies are probably the best way of all, thinking about them.

There is a huge area of emphasis right in that I think we can build on from the human epidemiology side, and that's in the whole area of causality. The kind of saying used to be, well, when you run an epi-study, it is an association. Association is not causation.

But now there is a whole science of causality to look at how you design the analyses and the comparisons to really tease things apart to come up with causal associations. So I think building on that whole area is going to be really important because ultimately we want to know if a drug causes a positive outcome, and that's the fundamental question. And then the size of that outcome, how big it is.

And so I think it's a rapidly expanding area that -- we might think cohorts are the best, and they probably are but there are other kinds of study designs that are being developed to do that.

And then I think another really important part that got discussed this morning are simulation studies. I think we can take what we know and use simulation to say what are the bounds of what we know, and where are the other pieces that we might need to plug in here together to get this final answer as opposed to saying we will have one study and it will answer everything.

DR. LUND: I guess what I would add to that, and

if I had one answer I would say prospective cohort study. And there is a great study that just got funded by the National Institutes on Aging using dogs as a model for longevity in aging in humans and it's based out of both Texas A&M and the University of Washington, Daniel Promislow.

And so it's a large -- they are planning 10,000 dogs to study in a prospective way, and they will have multiple studies sort of nested within that where, I kind of spoke to a hybrid design where you have a cohort that you are following before exposure, before outcomes are observed, and I think there is the most power in that.

There is definitely some effort and there is some research that needs to be brought to bear so you can truly follow up as many of those animals or if you are on the human side, humans. But I guess my one answer would be a prospective cohort with some sort of nested additional studies.

We talked about outcomes and how, depending on the question you've asked, you may need to have more scrutiny around the outcome assessment.

DR. SMITH: And our final question is what do you foresee as the biggest challenge to the use of real world evidence to demonstrate effectiveness or reasonable expectation effectiveness, which would be for conditional approval for animal drugs?

DR. LUND: I touched on it briefly. I really think there are multiple stakeholders in this sort of equations but there won't be the forces that exist on the human side in terms of government and health insurance and who is paying for health insurance.

And so I think it's time. Dottie, you said something about all hands on deck. I think really finding, having really thoughtful conversations across that stakeholder network, and that includes that's everywhere from the pet owner, the veterinarian, the veterinary team to animal pharma. What the value proposition is. And everybody has to realize some value in this process.

And we don't have the infrastructure and the momentum that's provided by funding either to control funding or to continue funding on the human side so I'm hopeful but it's going to be a complex navigation.

DR. HUNGERFORD: And I agree, and I think that idea of there are different stakeholders and different groups that can use different things out of the health records and so working together so that there is much more communication so that can move forward I think is critical because I think there are different camps now that just really don't talk to each other much, that go their own way.

And that means that each one isn't kind of augmenting and empowering the other. So I think that's one

problem. I think the other problem is that the CVM GFI is not out yet.

DR. SMITH: Thank you both. So we're going to move now to our registered speakers. And I will first invite our first speaker, Heather Pidcoke.

Public Comment

Heather Pidcoke, MD, MSCI, Ph.D.

Colorado State University

DR. PIDCOKE: I am Heather Pidcoke. I'm the Chief Medical Research Officer for Colorado State University. I'll just give my disclosure that I'm not a subject matter expert on real world evidence. And my desire to give some remarks is really based on a sort of unique place in time that I'm at right now, which is I currently just joined CSU, which is a big veterinary campus, and all my previous experience was in research in the human space.

So trained in surgery, worked for the military on blood research for damage control resuscitation. And then went to industry and worked on those same products trying to get them through development and now I'm in this sort of unique position of suddenly being thrown into the world of veterinary clinical development.

And I just had some thoughts based on that, and it really applies to both this session and the previous session. So I'm going to try to get to the things I wrote

down.

I first wanted to just commend FDA on addressing the challenges related to clinical trials and promoting innovation. I think that this is just phenomenal to have this group of people here to discuss these concepts and try to address some of the challenges.

I think there are a lot of challenges to be addressed, and so in the veterinary space, I think even more so than in the human space, funding is scarce and very difficult to come by. And this is a challenge that veterinarians really have to get creative to work around.

Data-gathering systems, as discussed by Dr. Lund and Dr. Hungerford, are pretty limited. You know, we think we have challenges on the human side of things and then you go to a veterinary hospital and you realize how many more limitations they're working with and what they're able to do despite that.

So for human use, as Dr. Hungerford alluded to, FDA has guidance for use of real world data, and they're developing guidance for use of adaptive clinical designs and innovative trial designs. That is not the case in veterinary medicine.

Most of the people that I have come across at Colorado State University, and I discuss adaptive trial designs, they've never heard of it before or they have a very

limited, you know, experience with that.

So I think there are a lot of challenges in bringing that over, from the infrastructure point of view and also from the point of view of just having a body of people who have experience in that area.

Finally, I think going back to the challenges with funding, adaptive design trials are not cheap and require simulations that are extremely expensive. So how are we going to address that in the veterinary space?

So I think there are opportunities that are huge. I think that linking veterinary clinical development programs to human programs in the areas where that compatibility exists could be one way of funding veterinary therapies by tying them as preclinical data to human therapies. I think that is something that really could be looked into.

But right now you have to be very, very motivated, very organized and have just a phenomenal team in order to make that happen because the barriers to it are extremely high. So my final thoughts to FDA as they consider all these topics is that -- is there anything FDA can do to reduce the barriers to that happening?

Is there any way that FDA could maybe get together with the human side of FDA and talk about, well, we have different metrics for human therapies but how could we help investigative teams overcome some of these and really,

you know, coordinate these efforts so that we get more out of the data that we do have?

How do we bring in real world data not only as the human side but as preclinical data to add to human development programs? So I commend FDA for the creativeness of these types of interactions but I also ask FDA to help all of us make these development programs more collaborative across species. Thank you.

(Applause)

DR. SMITH: We invite our second speaker, Terry Settje.

Public Comment

Terry Settje

Bayer Animal Health

MR. SETTJE: Thank you for the opportunity to provide comments on the use of real world data and real world evidence in clinical investigations for new animal drugs.

My name is Terry Settje from Bayer Animal Health. I am representing the Animal Health Institute. The Animal Health Institute foresees great opportunities in this space for the animal health industry. Permitting the use of real world data and real world evidence will further supplement several areas.

Four such areas include: Number 1, proposals for alternative study designs and possibly replace various aspects of typical or traditional clinical research trials.

Number 2, label changes to approve drugs, including adding or modifying an indication, changes in dose, dose regimen or the route administration, use in a new population and/or species, and updating safety information.

Number 3: post-marketing activities to support a regulatory decision including currently used evidence for pharmacovigilance activities and evidence to support conditional approvals. And 4, nontraditional pathways, such as adaptive study designs, the use of foreign data, qualifying biomarkers as surrogate endpoints, nonrandomized single-arm trials using real world evidence as an external control, and of course observational studies.

The FDA has indicated a desire to quote close the vital gaps between evidence generated using traditional clinical field trials and evidence leveraged from real world data including the use of foreign data.

Whether similar gaps are evident in the animal health industry or not, opportunities exist using today's technology to enhance the totality of evidence related to new animal drugs by utilizing real world evidence.

AHI stresses the importance of ascertaining relevant and reliable sources of real world data. For this reason, we recommend the guidance include decision support tools to assist both sponsors and veterinarian clinics in assessing relevant and reliable sources of real world data.

Permitting the proper use of real world data and real world evidence will increase the magnitude of substantial evidence of safety and effectiveness of a veterinarian drug or device. AHI supports the Center's endeavors to investigate and draft guidances for the use of real world data and real world evidence as part of FDA's new animal drug approval process. Thank you.

(Applause)

DR. ELLENBERG: Okay, folks. At this time we will move forward and adjourn for lunch and return promptly and 1:30 p.m., when we will get started. Those individuals who will be participating in the panel this afternoon for the first session in the afternoon, make sure you show up a little earlier so we can make sure everything works perfectly. Thank you.

(Whereupon, luncheon recess was taken.)

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

(1:31 p.m.)

Session 3: Biomarkers and Surrogate Endpoints

Phillip Turfle, Veterinary Medical Officer

Division of Therapeutic Drugs for Non-Food Animals

Center for Veterinary Medicine, FDA

DR. TURFLE: Good afternoon, everybody. Go ahead and settle down and we will get started on our afternoon.

I would like to welcome you to this afternoon's session. I am Phil Turfle, Veterinary Medical Officer in the Office of New Animal Drug Evaluation and I will be moderating this session. We've had some great talks this morning and hope to continue this momentum as we continue into our next topic area.

I'll try to keep my introduction swift and brief to allow our invited speakers and you as much time to provide feedback in how biomarkers and surrogate endpoints can be used in clinical studies for effectiveness.

As in the other sessions we need to define our terms. We'll begin by defining biomarkers and surrogate endpoints. These definitions come from the biomarkers endpoints and other tools resource more commonly known by the an acronym of BEST and it is published on line by the FDA-NIH Biomarker Working Group.

In summary a biomarker is a defined characteristic that is measured as an indicator of normal biological or pathogenic process or in response to a therapeutic intervention. Two examples, creatinine, which is commonly used as an indicator of kidney function, and glucose which is commonly associated with its use in diabetes mellitus.

A surrogate endpoint is an endpoint that is used in clinical trials as a substitute for direct measure of how

patient feels, functions or survives. As a substitute the surrogate endpoint is intended to predict a particular clinical benefit or desired outcome.

In animal drugs sperm count was used as a surrogate endpoint to show Zeuterin's effectiveness for the desired outcome of chemical sterilization of young male dogs. And so sperm count was used as the substitute for the dog's ability to sire puppies.

I want to know that the effects on how patient feels, functions or survives is how clinical benefit is evaluated for human drug approval because not all animal drugs provide a benefit or direct benefit to the individual animal, we request stakeholder feedback on how well this definition of surrogate endpoint applies to animal drug regulation.

Biomarker activities outside of CVM of which we are aware include BEST, which we've already mentioned, the Center for Drug Evaluation and Research's Biomarker Qualification Program and the two consortia here, the Biomarker Consortium of the Foundation for the NIH and Critical Path Institute. Both of these bring together academia, researchers and regulated industry to develop and ultimately qualify biomarkers though CDER's Biomarker Qualification Program.

And I just want to point out that this would be

another -- a good time to highlight the all hands efforts that have been mentioned this morning as far as bringing together and creating consortium. We would certainly love to see the same thing in veterinary medicine.

So, in the Federal Register Notice we posed five questions.

(Slide)

Question 1, what are your expectations for the use of biomarkers in the context of animal drug regulation and how might biomarkers be used in the design and conduct of clinical studies beyond their use of surrogate endpoints.

(Slide)

Question 2, what information to be provided to the FDA to support biomarkers use in diagnosing disease, to enroll patients, sample size estimations and pilot/proof-of-concept studies.

(Slide)

Question 3, what are the major challenges in translating potential biomarkers and/or surrogate endpoints into practical tools in clinical trials and what are possible solutions to these challenges.

Question 4, how do we determine the evidentiary criteria for evaluating biomarker use.

(Slide)

And Question 5, should the FDA's Center for

Veterinary Medicine develop a biomaker qualification program like CDER's, would such a program be beneficial and is it something that stakeholders are likely to use, are there other approaches in development and acceptance of biomarkers for animal drugs, that CVM should consider.

(Slide)

As I stated previously, your comments are greatly appreciated.

(Slide)

If you are not able to provide your comments today, we sincerely encourage you to provide your comments to the docket which will remain open until August 17, 2019.

(Slide)

I would like to introduce our speakers and panelists today. We have Doctor Hans Coetzee from Kansas State University. Doctor Lisa McShane from the National Cancer Institute of the National Institutes of Health. Doctor Chad Ray from Zoetis, Inc. And Mr. Terry Katz from Merck Animal Health.

And so the first three will be providing presentations and then Doctor -- they will be joining Mr. Katz in the panel discussion.

So, I would like to turn it over to our first speaker, Doctor Hans Goetzee.

Invited Speaker No. 1

DR. COETZEE: Thank you very much. I appreciate the opportunity to be here this afternoon and visit with you about some of the research that we have been doing evaluating biomarkers for pain assessments specifically in livestock.

(Slide)

The goals of my presentation will be to talk about some of the potential biomarkers for studying pain in livestock and how those biomarkers may be useful in the approval process of analgesic drugs in food animals. The last topic that I will discuss briefly are some of the major challenges that we have in translating those pain biomarkers into practical tools.

(Slide)

To start off the definition of pain would probably valuable and this is the accepted definition, working definition for pain in animals, is an aversive feeling or sensation associated with actual or potential tissue damage resulting in a physiological, neuroendocrine or behavioral change that indicates a stress response.

So, based on the definition, it is clearly three areas where we can investigate potential biomarkers and that is in the physiological changes associated with pain, the

neuroendocrine changes associated with pain and then the behavioral changes associated with pain.

The challenge we have in animals, especially livestock, is that pain has both a sensory and affective component. The affective component being primarily emotional and very challenging obviously to assess in a non-communicative animal.

Most of our production species have also been bred or come from stock where the expression of pain is disadvantageous to the animal being a prey species. And so most of our livestock do their very best to try and conceal signs of pain.

(Slide)

In terms of common pain models in livestock production systems there are many. And these are examples of some of the conditions that exist in production system currently where pain mitigation would be beneficial.

The first of these would be elective procedures, and that includes castration, tail docking, dehorning, beak trimming in poultry and branding practices in which some states that's still a requirement.

Other painful conditions that we encounter in livestock production systems would be lameness, calving, lambing and farrowing. There continues to be some discussion in livestock production whether these conditions are painful

and how we would assess pain in these conditions, and more importantly whether animals would benefit from receiving analgesia following these conditions and some of that research is ongoing.

But clearly there are many opportunities for us to use analgesia in livestock production systems. For example, we had produced 133 million piglets in the United States each year and there are about 10 million castration, tail docking or castration dehorning procedures that are performed in cattle each year. And so this is a very common practice in production systems that would clearly benefit from the use of analgesia.

(Slide)

In regards to the approval of analgesic drugs for use in livestock, this has been extremely challenging for us, specifically FDA Guidance 123 in Section 6, under Labeling, states that we, the FDA, recommends that this indication be based on the control of clinical signs of pain associated with the disease, and FDA encourages the use of validated methods of pain assessment in the target species. And that's been a very significant challenge for us, both in the research and the production systems, is finding those validated methods of assessment.

In July of 2017 a drug was approved for relief of pain associated with foot rot, and it was assessed using a

novel pressure mat system which was the first drug approved in the United States with analgesia on the label which was a very significant milestone.

(Slide)

So, how do we know if it hurts. This is a little like the producer asking the chicken what are you talking about, just lay eggs and the chicken says no, I want an epidural. It's not quite as simple as that in terms of assessing pain in our production species.

(Slide)

So, what are the properties of the ideal biomarker. They are specific to pain and responsive to analgesic drug administration. It can be quantifiable in samples that are relatively easy to collect and where the timing and method of sample collection does not confound the experiment.

This is something that we have significant challenges with in production systems is being able to collect a sample in a way that the act of collecting the sample doesn't in fact confound the biomarker we are trying to collect. And particularly cortisol would be an example of a biomarker that is susceptible to that.

The biomarker needs to be robust, stable and reproducible and predictable across different natural and experimental painful conditions. And the analysis of that

biomarker should be accomplished using a validated analytical method.

(Slide)

These are some examples of the biomarkers that we currently are trying to validate for use in livestock species. These includes the use of thermography up in the top right-hand corner. Pressure algometry in which the application of pressure to a painful site elicited a behavioral response which allows us to determine the mechanical nociceptor threshold of the animal. Heart rate determination, in this case with a Polar Heart Rate Monitor which is the watch there in the middle. And the assessment of substance P, has been an area we've also examined to try to assess pain in livestock.

In addition, we've done some work with EEGs, in the middle right there. We've done some assessment with cortisol in the bottom right corner. And then we've done some work with chute exit speeds, so the speed in which the animal leaves a processing facility through the use of barrel racing timers. And then in the bottom left-hand corner -- or right-hand corner, sorry, is the pressure mat that we talked about previously that was used for the approval of Banamine Transdermal. And then the middle is the use of accelerometers, which we've also studied to tried to validate as pain assessment biomarkers.

(Slide)

In terms of how these biomarkers have performed in terms of their assessment, the ones that I've highlighted in red there, we've had challenges with and that's been the use of electro-dermal activity, chute exits speeds, growth and performance and accelerometers. In those conditions we've had several examples of and studies where those have not performed as expected.

The ones in yellow in the middle, behavior, heart rate determination, plasma cortisol, substance P, EEGs and mechanical nociceptor, we've had some variable results where there have been experiments where they performed extremely well and other experiments where they have not.

And then the use of thermography and pressure mat analysis have been more reliable, at least in our hands, in terms of pain assessment although with thermography we still have some challenges using that as an assessment tool specifically looking at ocular thermography in animals and I'll show you some data here in the next few slides.

(Slide)

So, what I want to focus on for the rest of this presentation is how these biomarkers might be useful in the approval process of analgesic drugs in food animals.

And I present to you here three experiments in which we used the same analytical methods to assess cortisol,

substance P, and some other endpoints, they were conducted in the same lab. They all used the same drug. The transdermal flunixin meglumine, and they are assessed three different painful conditions in food animals.

And one of them was castration, the second was dehorning and the third was an induced lameness with Amphotericin-B.

So, with all three of these studies using the same endpoints and the same laboratory and the same drug with the same dose, it gives us some opportunity to be able to do some comparison between some different painful conditions and some different studies to try to evaluate these endpoints using a receiver/operating characteristic curves or ROC approach.

(Slide)

So, in comparing the biomarkers using a receiver/operating characteristic curves we were essentially creating a graphical plot that illustrates the diagnostic ability of a test as discrimination thresholds are varied.

So, as we vary cutoff points for the test we can plot these curves, which essentially plot true positive rate on the Y axis with false positive rate on the X axis. And it gives you an opportunity to assess the area under the ROC curve which is an indication of the predictive value of a biomarker.

So, the ROC is created by plotting the true positive rates or the TPR against the false positive rate in assessing the different thresholds that you are testing.

So, in this particular example here the red line is random, green is a good test, orange is a better test, and blue is the best test. So, the more the line tends towards the true positive rate on the Y axis the better the test performs and the higher the AUC will be.

(Slide)

So, there have been several examples that we've conducted in our lab using those three papers, where we looked specifically at cortisol after castration, at three different time points. And in this particular slide we're comparing no pain versus pain and we're comparing pain versus analgesia. And you'll note there the different area under the curve measurements are given and we also got the different cutoff points are given.

And so when you're looking at one hour after castration of cortisol you've got an AUC of 0.98 which is -- would be considered excellent. But because 0.9 and 1, is the desired area under the curve that you want to get for an assay, but if you were take a sample at four hours, the AUC would drop to 0.96. If you took it at twelve hours it would drop to 0.51.

Similarly, if you looked at pain versus

analgesia, this across those three studies, you start off with an AUC of 0.75 at one hour. The AUC improved to 0.9 at four hours. And then it drops back to 0.87 at twelve hours.

So, the take-home message from this particular experiment is that varying times can vary the outcome of the test and so can varying intervention. So, if you are comparing pain versus no pain or analgesia versus pain, those interventions can all vary the outcomes in terms of optimizing the timing and the area under the curve of this particular sample collected after castration.

When you look across the three different painful interventions, we got castration, dehorning and lameness. All standardized at six hours. Again we're comparing no pain versus pain and pain versus analgesia, you'll note that in castration at six hours, no pain versus pain, the AUC is 0.91. So, the test is very good discrimination of animals that are in pain versus no pain. But when you are looking at animals that are in pain versus those in analgesia the discrimination is not very good. It is only 0.71.

Similarly, when you're looking at dehorning in both the pain versus no pain and the pain versus analgesia, the discrimination is only 0.7 at those different cutoffs.

And in lameness when you're comparing those two, the discrimination was only 0.45, which is extremely poor in comparing pain versus no pain. But when you are looking at

analgesia versus pain the discrimination was better at 0.85.

So, again these types of data could be extremely useful for a sponsor in trying to optimize which time points to collect samples in addition to looking across different processes and procedures to figure out which of these would be the best in terms of assessing this particular drug against this condition.

(Slide)

I have some different examples here. And this is where we've plotted the AUC over time. And the red line here would be pain versus no pain and the blue line is analgesia versus pain. And you'll note here for castration that we had very good test performance above the 0.7 through to about eight hours after the process. But when you looked at dehorning there was much poorer performance of the test.

And when you looked at lameness only -- differentiation between analgesia versus pain performed well when using cortisol as an endpoint. When you used the pain versus no pain discrimination the AUCs were generally very poor in conditions of lameness.

So, it varies by condition, it also varies by time point.

(Slide)

Similarly when we looked at substance P the overall, the performance of the assay was very poor when we

plotted ROC curve areas under the curve under time. And what we found was only for lameness did we see the ability of substance P to be used to distinguish pain versus no pain and that was out to about -- from about twelve to forty-eight hours after the lameness was induced. But overall substance P was very poor at distinguishing analgesia versus pain through all three of those different experiments.

(Slide)

When you looked at infrared thermography comparing the area under the curve using again ROC curves over time we found some variation that occurred over time and this was just in the dehorning and the castration experiment, that two that we used, AUCs under ROC. And we found that only at forty-eight hours did infrared thermography performed satisfactory. And when we looked at castration it didn't perform very well at all over time, except at a single time point of twelve hours.

So, a lot of variability around infrared thermography which made it quite difficult to assess.

(Slide)

When you looked at mechanical nociceptor threshold the assay test worked very well for distinguishing pain versus no pain but struggled to distinguish pain versus analgesia except at forty-eight hours after the procedure where it performed satisfactorily above the .7 area under the

curve for that particular biomarker.

(Slide)

And then finally when we looked at the pressure mat, the pressure mat actually performed extremely well for distinguishing pain versus no pain and pain versus analgesia out through about seventy-two hours after lameness was induced, but Amphotericin B induces a very transient lameness and so the issue with that is over time the animals are going to become less lame because the lameness does not persist throughout the lameness process. And so that's why that test started to perform poorly after 96 hours.

(Slide)

So, to finish up I just wanted to highlight some of the challenges associated with translating pain biomarkers into practical tools.

The first one of these is with cortisol is we have the circadian rhythm. So, the top graph demonstrates circadian rhythm of cortisol in calves over time. These animals were not subjected to any painful procedure and you'll notice there was a peak in cortisol at one o'clock in the afternoon and again at five o'clock in the morning. And that persisted over a forty-eight period of time.

You'll also notice the two calves at the bottom. One of those was subjected to a sham procedure followed by dehorning and castration. And spiked a very significant

cortisol response after dehorning and castration.

Whereas, in the second calve, the graph closest to me, which would be on your right, the animals that were subjected to the sham procedures spiked a cortisol response which also was evidence after dehorning and castration. So, in that example cortisol was not very specific to the painful process.

(Slide)

The other challenges, specifically with substance P was stability at room temperature. The substance P is very rapidly degraded. We lost about 30 percent of the spiked substance P in a cooler and 70 percent on the bench within the first hour after sample collection. And that creates some significant challenges in terms of the field application of that endpoint because of the very rapid degradation of the substance P over time.

(Slide)

And finally with the mechanical nociceptor threshold we find that animals become habituated or acclimated to people approaching them and so we start seeing some variability between horns and variability between sites, when we try to assess mechanical nociceptor threshold in these animals using a pressure algometer. And so these tools are far more useful for assessing a single time point, a lot more variable when assessing multiple time points after the

procedure.

(Slide)

So, in conclusion then the validated biomarkers of pain in livestock would expedite the approval of analgesic drugs. We have yet to identify a single biomarker or pain assessment in livestock and most of those that we worked with have several deficiencies. However when combinations of those biomarkers are used, we typically get far more reliable results.

We found that ROC curves may have value in identifying the potential utility of a given biomarker or set of biomarkers to optimize the timing of sample collection. And we are currently evaluating some new genomic approaches to assess gene expression associated with pain and inflammation in livestock that may have value at identifying more robust biomarkers for clinical applications in the future.

(Slide)

I appreciate your time and attention. I would also like to acknowledge support we received from USDA in funding our research and several graduate students that have been involved in these projects. And I will be happy to take any questions now or in the panel station of there are any.

(Applause)

DR. TURFLE: All right. So, I'd like to invite

up our second speaker, Doctor Lisa McShane, from the National Cancer Institute and the National Institutes of Health.

Invited Speaker No. 2

Lisa McShane, Ph.D.,

National Cancer Institute, National Institutes of Health

DR. McSHANE: Thank you. I would like to thank the organizers for inviting me to this. I do not work in veterinary medicine. Although I did my Ph.D. work at Cornell and so my introduction to epidemiology came from their vet school.

I now work at the national Cancer Institute. I collaborate a lot with the folks at FDA and to the point that many people have the mistaken impression that I work for the FDA. But I do enjoy working with them.

(Slide)

I have no disclosures as any Federal employee will tell you.

(Laughter)

(Slide)

So, one of my biggest collaborations with my colleagues at the FDA has been in the development of the BEST resource and in particular the glossary that you've heard about already a couple of times today. I work in the field of cancer therapeutics and my specialization is in fact biomarkers.

So, we use biomarkers all the time in cancer, all of our therapies now, virtually are driven by biomarkers. So, I just live it and breath it every day.

I want to make a couple of distinctions between biomarkers used for drug development, which is much of which we have been discussing today, versus clinical use. And there is an important difference there. Difference in the kind of evidence you need to accumulate, what requirements you have over the biomarker assay or test.

You heard a wonderful presentation this morning from Bob Temple about biomarkers used for clinical trial enrichment. So, I'm going to really gloss over those slides. But I do want to elaborate a little bit more on another use of biomarkers, surrogate endpoints which we've touched on bit today, but I want to go into a little bit more detail from a statistician's prospective.

(Slide)

So, you already heard the definition of biomarker. I want to emphasize the last part of this paragraph, that we really can think of biomarkers much more broadly then just sort of a biochemical measurement. They can be histologic measures, even radiographic measurements or other kinds of physiological characteristics.

Really the kind of evidentiary approach you take is not that sensitive to what type of biomarker is. It's

more sensitive to what you are trying to establish about the biomarker. Where it can be useful and in what context.

(Slide)

So, prognostic and predictive biomarker, you already heard about use of those for clinical trial enrichment. But I want to take just a couple of minutes to make a distinction between clinical use of prognostic and predictive biomarkers and use of these types of biomarkers for clinical trial enrichment.

And we run into this a lot in oncology. You have to appreciate that often when you have a drug that you think will work best in a particular biomarker defined population, for purposes of the clinical trial you may not have that biomarker refined sufficiently to say this is going to be the ultimate clinical test I will use to guide use of the therapy if the trial is successful.

The idea of enrichment is you want to get close enough. You want to get, you know, more of the patients in your clinical trial that are most likely to benefit from the drug than just taking an all comers approach. So, it will help you from a statistical prospective as Bob explained for the prognostic biomarker you are trying to enrich for patients, or in your case animals, they are more likely to have the event you are interested in.

And what that does for you statistically is that

whenever you have a time to event kind of endpoint like survival or time to, you know, pain relief, time to whatever, that your statistical power depends on the number of events. It doesn't depend on the number of samples size. It depends on the number of events, which is why if you have a kind of study in a very low risk population, where let's say in some kind of fairly indolent disease where you get some patients having a negative outcome but many won't.

That kind of trial would have to be much bigger in order to have the same statistical power to detect a treatment effect than if you had a population that had very poor prognostic factors for predicting what you are trying to do is enrich for sort of the magnitude of the treatment effects. So, you're saying you are hoping that more of these patients will have the potential to benefit from the treatment. If you mix in a bunch of other patients who don't have the special biomarker that indicates that they will most likely benefit from the therapy then your treatment effect in that overall trial population is kind of a deluded version of treatment effect.

You know, it is a bunch of patients who aren't going to respond and then a bunch who will respond but the overall effect gets kind of muted.

So, that's the idea behind the prognostic and predictive biomarkers. So, in the one case you are trying to

get more events which increases your statistical power. In the other case, for the predictive biomarkers you are trying to get a larger effect size because that effect size has been deluded to some extent by the ones that don't have the perfect biomarker.

(Slide)

Also want to talk a little bit about pharacodynamic and response biomarkers. And these are often confused or I should say mistakenly referred to as surrogate endpoints. Some of them will turn out to be good surrogate endpoints. But the fact that they indicate a biological response does not necessarily mean that that biomarker would be a good surrogate endpoint. And I will explain that. I know it sounds sort of counterintuitive. I have a little example that will hopefully make this clear.

(Slide)

I also need to make the clarification that I will be using the word biomarker pretty freely throughout this talk. But in fact a biomarker has to be measured to be useful. Okay. And there are many different ways we can measure a biomarker. You know, in cancer, for example, we have many immunohistological tests, you probably use them in veterinary science, as well.

But the particular antibody that you use in that immunohisto-chemical test may lead to very different

positivity rates. Other factors, like how you process the specimen may effect your downstream test result.

So, this is why in the BEST glossary you'll find we define the term biomarker test and we say that it really has three components. You need to first of all have the materials for measurements. So, that might be your equipment it might be your antibodies, you know, all those kinds of things, your probes.

And then you have to have an assay for obtaining the measurement of the biomarker. So, you need to have sort of a recipe, how do you go through this procedure, what is your experimental protocol in order to come up with this measurement. It's not sufficient to say well, I just have this antibody but apply it however you want.

And then there is the method or the criteria for interpreting those measurements. Often an assay will be putting out some kind raw value. You might do further proof processing of that value. You might be combining that value with values of other biomarkers into some kind of score. If it is a continuous measurement that comes out of your assay you may apply a cut point to say well, this is what I'm going to call positive, this is what I'm going to call negative.

So, all of these factors are important in how you get that end result for your biomarker. And therefore, how well that end result biomarker value is going to correlate

with some other kind of endpoint you are interested in that will be important for your drug development program.

(Slide)

So, there -- I can't tell you how many times I've have been invited to give talks on the topic of biomarker validation. Okay. I say well, what do you mean by validation. And validation for what purpose. And so we have this lengthy discussion and eventually we get down to what they really want to hear about. But I thought it was worth making this distinction for you.

So, the first kind of validation we should talk about is analytical validation. So, this simply says can the biomarker test evaluate the biomarker in some acceptable way. Now, how do you define acceptable. It depends on the nature of your biomarker. It might mean is it sensitive, is it specific, it's accurate, does it have a nice linear, big linear range, is it precise, you know, whatever is relevant to your situation.

But you have to know that you are measuring this biomarker with your test in somewhat of a reliable or trustworthy way because if you have a horribly inaccurate test, you can expect that your biomarker is not going to correlate very well with other kinds of endpoints you are interested in because there is simply too much noise introduced by the lousy assay.

And again I would stress that this includes any kind of pre-analytical factors that are important or that will influence your biomarker result. So, does your specimen have to be quickly frozen. You know, we just heard about, you know, if you did not get that thing processed quickly your analyte would degrade and you just wouldn't be able to measure your biomarker. So, this all have to be considered early on in the process as you are developing a biomarker for some kind of use.

Clinical validation is what you'll see in many published articles. It simply says we are able to show that this -- the result that comes out of this test identifies, measures or predicts some concept of interest. Well, concept is just a fancy word for something like a clinical or biological or physical characteristic. So, in other words there is an association.

If you see a published article you are going to see P-values saying, you know this is linear related to this or this -- the area under the curve is greater, significantly greater than point five. So, those are all establishing associations. But simply having association, even a statistically significant association is not necessarily sufficient to make your biomarker useful for your purpose.

(Slide)

Now here we sort of get into the distinction

between drug development tool and clinical use. So, in the clinical world in which I live mostly we talk about clinical utility of a biomarker test. So, this would be a biomarker test you are going to use in your clinical practice, and you can rely upon it to have a particular interpretation that allows you to manage the care of that patient. And the net result is that the patient will have a better outcome because you used the biomarker.

So, it might be that the biomarker tells you to give treatment A instead of treatment B, it might say this patient has an excellent prognosis and their illness is likely to just resolve on its own, you don't need to give any treatment, that would be a prognostic kind of biomarker. So, those would be clinical uses. So, the bar for clinical use is going to be generally higher than the bar for use of a biomarker in drug development settings.

(Slide)

The term qualification is one that we use in the context of drug development tools. So, something like an enrichment biomarker. So, just how well does that biomarker have to perform if you want it to be a prognostic enrichment tool for running a clinical trial. Well, it has to increase the number of events that in the population identified by the biomarker. But it doesn't necessarily have to be, you know, ninety percent sensitive or ninety-nine percent sensitive.

It only has to be good enough that it gives you some benefit to give you more efficiency in your drug development program.

So, this is -- I find that in the academic communities that I work with there is a lot of confusion about this. They hear the term biomarker qualification. They hear the term validation. They completely confuse them all. And nobody actually understands it so I am making an attempt here to clear it up a little bit.

(Slide)

So, the medical product development tool used for the qualification process, as I think everybody here knows, there is a formal FDA program, qualification program. But I should mentioned that use of a -- that use of a biomarker in an individual say drug development program, can still be okay if you do it in consultation with the FDA, you do not have to qualify a biomarker in order to use it in your individual drug development program. And there may be FDA people here who want to elaborate on that in the discussion session.

But it's saying this is an opportunity, qualifications program is an opportunity to get sort of a more, I would say broad blessing on a biomarker where it could be -- you are kind of sharing information, you could use it in more than one context if the qualification covers that whole, you know, range of use. So it's just a little bit of doing your homework and getting a little bit done so

that you can leverage what you have already done with the biomarker.

But that's not to say that you might not have a very specialized biomarker for a new drug in a new class that you're developing. It doesn't say you cannot use that biomarker. Just, you know, consult with FDA and make sure they are comfortable with how you are using it, how you are interpreting it.

(Slide)

So, I guess I already mentioned this. The clinical utility really it's the idea of risk/benefit tradeoff. Are you better off using that biomarker in the sense that your patient will have a better outcome.

And I have to say there are plenty of biomarkers in, you know, human being medicine that doctors use all the time and they may only get a kind of gestalt from them and decide well, hum, this kind of looks good. I am not going to worry too much about the patient. But they may not actually be using it very directly for changing clinical care. And so those are always kind of difficult and it would be a whole session for another day on CDRH and how they regulate these kinds of biomarker tests and it really is all linked to the claim that is being made with the biomarker.

So, you can get a clearance for example for a biomarker test for something that says well this is a

prognostic biomarker in a case prognosis and maybe it should be used in combination with other clinical and pathological factors to do this or that, you know, that's a different kind of claim than okay, we have this drug and we've shown that it's efficacious compared to standard therapy. So, it's all, you know, very tricky labeling.

(Slide)

So, I'm going to skip this because Bob did such a great job this morning, already explaining this, the idea of enrichment. So, let me move on to surrogate endpoint biomarkers.

(Slide)

So, I will remind you the definition, it's an endpoint that is used in clinical trials as a substitute for a direct measure of how a patient feels, functions or survives. Here is the basic idea in a nutshell. Okay.

We want to be able to look for a difference on our surrogate endpoint and have that be a good predictor of the difference we would have seen or the treatment effect we would have seen had we carried that trial out to fruition to see the sort of definitive or true or regulatory accepted clinical benefit endpoint. Okay.

So, here I am. I say okay. Well, suppose I have a binary biomarker and I show that on treatment A I get fifty percent positive for the biomarker, after I give the

treatment. Treatment B at seventy percent. I would love to be able to say well, if getting positive we think is a good thing I would love to be able to say I do not need to follow this patients the whole way out to, you know, death. That I know because of my biomarker, if I trust my biomarker, that that means I can quit here and declare that treatment B is better.

Well, it turns out that's a very, very tricky thing to do. And I am going to show you a little numerical example to explain why that is.

And I should add that, you know, the reason that we measure these biomarkers of course, is that we can usually get them sooner, more easily, less invasive or perhaps less expensively. You may even have like a procedure that's very invasive, to determine your definitive endpoint.

So, if you had a biomarker you could measure with a blood draw, that would be an advantage even though it might not save you in terms of number of patients, length of trial, that's still kind of benefit that you could experience from a biomarker surrogate endpoint.

(Slide)

We had a whole workshop, almost exactly a year ago, talking about evidentiary criteria for establishing surrogate endpoints. And again, this is a very, very tricky subject. And one that FDA is still having lots of dialogue

about. But we -- in this working group, to which I was also a member of, said that there are kind of five basic things you are looking for, for a surrogate endpoint. You want to have causality, you want to have ideally your biomarker surrogate endpoint would be on the causal pathway to your disease endpoint. Okay.

So, everything has to travel through that biomarker, that's the perfect situation. Unfortunately that's not the way the world works usually. Think about drugs. They have off target effects. They may not work exactly the way they think it works. So, we might be not quite on the right path, that causal pathway. Lots of things can happen.

You know, we want to have some kind of plausibility of the biomarker. We don't want to just go data drudging and fishing up something that seems to correlate with our endpoint. It really helps to have some biological plausibility.

We want it to be specific. And -- and be -- understand what complicating effects there may be. So, I already mentioned things like off target effects of the drugs.

Proportionality, we'd like that the magnitude of change on that biomarker would be nice, if that actually correlated with the magnitude of treatment effect on your

definitive endpoint.

And we need to worry a lot about universality, so something that's a perfect biomarker -- surrogate endpoint biomarker in one setting for one class of drugs, for one species of animal, doesn't always transfer to another. So, you're always having to make some degree or extrapolation or leap of faith as to just how far you can push the envelop once you have established something is a good biomarker or surrogate endpoint in a particular setting.

(Slide)

And to confuse things more, and I hope I can go just a couple more minutes -- okay. Confuse things more we statisticians have not helped things because we've used terminology that's been very confusing. So, there is this concept of individual levels surrogacy and trial level surrogacy.

What we're really talking about when we're talking about using surrogate endpoints in drug development, is trial level surrogacy, because you're looking at a trial level result, the effect on the biomarker in your trial, you want that to predict the trial level result on your definitive endpoint. Okay.

But what is too often mistaken as the ideal kind of biomarker is what sometimes is referred to as individual level surrogacy, which means that sort of within an

individual it's basically prognostic for your endpoint. And let me show you why that can get you into trouble.

If you think that's all you have to show, for example if the patient has a response that they will then live longer, that's nice and it's prognostic, but it doesn't get you the criteria that you need for a trial level surrogate. And here's the example why that logic breaks down.

(Slide)

So these pictures that I have here show the -- suppose we have a two-arm randomize trial. And on the one arm we get a sixty percent response rate, on the other arm we get a forty percent response rate in green there. So, we know that if you get a response you have a better event free survival, therefore it must be that treatment A is better than treatment B.

Well, here's the flaw in the logic. What we don't know is that the responders under treatment A behave the same as the responders under treatment B. And the same for the non-responders. Okay.

So, what I've shown in the table there are different relationships between response and outcome depending on the treatment received. Okay. And all of those examples, the response is prognostic for event free survival but I can come up with an event free survival difference

comparing A to B that ranges from negative ten percent to positive twelve percent. Depending on how those relationships differ according to treatment received. And that's where everything breaks down.

(Slide)

So, this is just a picture. And then I have to wrap up. Phil is ready to jump out of the chair and pull me off the stage.

So, what you need to be doing if you really want to show something is a reliable trial level surrogate is to do a meta analysis of trials. You have to plot whatever your treatment effect is on the definitive endpoint. In this case I've shown it as event free survival log has a ratio and then on your X axis it's going to be your biomarker effect which in this case as I've shown it is a log odds of biomarker response.

And in this particular case because low hazard rate is a good thing, we want to see a negative slope on that line. The different bubbles correspond to different trials. The size being the size of the trial with actually the number of events in the trial. Okay. So, that's the kind of analysis you need to do.

And you can imagine the challenges in that. Right, because you need to have multiple studies to do that. But the flip side is if you don't do that, if you think you

can do it looking only at a single trial, you run into this problem of prognostic not always implying good surrogate endpoint. And you have to bring in additional biology and cross your fingers and hope you are making the correct leaps of faith. But it's in general a very challenging problem. And Bob gave some very nice examples of catastrophes that happened with what people thought were good surrogate endpoints.

(Slide)

Okay. I will skip over this. Basically I am saying, you know, be consistent in your terminology, because you can't align the evidence if your definition is a moving target. Qualification and validation may be very context dependent. Consult with the FDA early and often, whenever you are trying to do something with biomarkers. Thank you very much.

(Applause)

DR. TURFLE: And so I'd like to go ahead and invite up Doctor Chad Ray for the next presentation.

Invited Speaker No. 3

Chad Ray, Ph.D.

Zoetis

DR. RAY: Yes, thank you to the organizers, and I'd also like to thank my colleagues from Zoetis that contributed, and finally some of the biomarker sub-team

within AHI that contributed to this talk.

(Slide)

So I'm going to follow up with what the last two speakers have provided and there is a lot of consistency. So, it's good that we really didn't have a change to share our perspective but we're pretty well aligned, so that is good.

So, what I did, the approach I took my expertise is in analytical validation, if you think about the biomarker continuum that we just heard described. I could've given a talk on that but I thought that would be a bit esoteric for the audience. So, rather than do that I looked at the five questions that were given in advance and I tried to build a story around that. And I also reorganized them around where I thought they were easier to answer and then with a little bit more difficulty to the end.

So, you will hear these questions asked again by the panel. So, I may speak a little less during the panel discussion, I guess.

(Slide)

So, the first question that I brought forward was, the question was should biomarkers be used in animal health. And I think the answer is absolutely. They provide an objective approach to defining efficacy and safety. You've heard a lot today about the potential improvements in

trial designs, speed, subjects.

Perhaps the most beneficial aspect though is the fact that biomarkers are objective measures in conditions of pain. We heard a perfect example there, well-being and mood. You can't ask the animal how they're feeling unlike you can in human subjects.

I should make the point too that in my intro I did I had twenty years of human biomarker experience, just the last two years I have transitioned into animal health, so. I found that applying biomarkers, like I said, is really an important aspect in animal health.

And so lastly, I guess, on this I would say novel biomarkers provide a better understanding then currently available tools. So, we're certainly investing in novel biomarkers.

(Slide)

So, another question that was asked was should the FDA develop a biomarker qualification program like CDER. I think the answer is yes. And rather than create -- the point I'm trying to make here is that many of these things have already been done by these various groups that are outlined here, the Critical Path Institute for example, spearheaded the biomarker analytical validation. Of course, the Foundations for the National Institutes of Health worked out the evidentiary criteria.

(Slide)

And then the outcome, as we heard, was the BEST document, which if you haven't, I know we've heard it described a couple times, but I can you that we at Zoetis are using this now, this Glossary. And we've heard, to be able to speak to the same language is essential in the field of biomarkers. This was originally presented by Christopher Leptak at the critical path discussion two years ago here in D.C.

So, we had a nice discussion previously by Doctor McShane on the various definitions. I think the three that we typically focus on were the ones that she outlined. Specifically in my group we pay a lot of attention to pharmacodynamic markers, to help us establish dose. And then give us the best probability of seeing success in later trials. But in addition to that we like the idea of predictive markers. We heard examples of enriching the populations to give you a better probability of success.

And then finally monitoring markers, whereby if you have a marker that would allow you to see changes over time, serial measurements, that would give you a better idea of whether or not the therapies are successful or not. So, those are the three we pay attention to.

(Slide)

I also agree with the concept of context of use.

Again if we're going to put a biomarker qualification plan in, a context of use is essential. As you can see from the definition it's a concise description of the biomarker's specified use in drug development. It has two components. So, that again refers back to the best definition. You have to define the category and then how are you going to use that test in drug development. So, each biomarker qualification effort should certainly identify one single context of use.

And one thing that I would mention that we talked a lot about at the critical path meeting two years ago was that each test, depending on how it's developed, is then associated with that context of use. So, just because you have say an analyte target, IL-6 for example, and you wanted to use that as a biomarker, you would have to show that the new test, if you developed a new test, didn't use the same one, had the same exact performance characteristics. You would have to go through the process. So, this is where the two are tied or interlinked.

(Slide)

So, the recommendation again it is apply common language to biomarkers based off of BEST, wouldn't change that. Context of use certainly needed. And then the evidentiary based qualification framework exists, so I'll talk about a little bit about that in one of my last slides.

But I think the one point here that has to be made about the differences is that we have to consider the limitations of animal health trials and establish appropriate incentives to realize the value of biomarkers.

Now, we also heard the potential with for false discovery, if you will, from a surrogate endpoint. I think this is going to be the major challenge that exists in animal health, is how do we -- how do we find the right level of evidence versus risk. And because what we don't have if you look at the LDL cholesterol and statin example, that was 94,000 patients in order to develop that sort of qualification. So, that's a challenge.

(Slide)

So, one of the -- another questions was what are the major challenges in translating potential biomarkers or surrogate endpoint into practical tools. I took a little bit different approach to answering this question.

And I would start with, in the lower right-hand corner, this is the approach that we're taking within our biomarker group. We start with the idea of maybe something from the literature where a marker has shown relevance or efficacy or we may use a genomic proteomic approach to develop a marker. Then we build an in vitro test, we validate it to some level of rigor to allow us to test in both laboratory models and non-interventional studies, to get

a sense of things like the robustness of the assay, the clinical relevance, the variance in the disease population to establish some of those cut-points we heard described using the receiver operator curves.

And then perhaps the most important component is to understand the collection processing and analysis or correlation with outcome that we can do in the POC studies.

(Slide)

Because as one of the speakers just mentioned this is a real challenge in animal health and it really starts -- and this is my prospective compared to human health, we actually have even fewer available equipment and technical skills at the clinics, for doing some of these biomarker assays.

So, the markers have to be extremely robust. You cannot have contributions of things like platelets or the wrong anticoagulant. They have to be processed appropriately. They have to be stable, we heard that example. And then there is also the balance that has to exist between the patient treatment and the biomarker needs. And this not unique to animal health. This is certainly a case in human health whether to take that serial biopsy, is it ethical. So, we have to weight these considerations.

And then, of course, another difference for animal health is that there are a lot of -- often times there

are plenty of reagents in human health to build test systems. And in animal health that's not always the case. So, that requires some up front work and actually development by the sponsor.

But I guess the take home message is we do believe biomarkers can be effectively implemented with the proper commitment and planning.

(Slide)

So, you heard this -- so, what information should be provided to the FDA to support biomarker use in these contexts. So, this is the what I think of as the three part process for truly demonstrating the relevance of a biomarker.

It starts with analytical validation. There is no point in testing a biomarker if it is in fact a test that lacks the appropriate rigor. Once you have that test then validated it's appropriate in a prospective study to test it to determine if there is in fact a correlation or connection between the disease outcome and the test itself. And then finally the idea of putting this test into practice, into the broader medical community to see if it will hold in, you know, in a large less controlled environment.

(Slide)

So, how to validate assays. These are a couple of references I put in. The other one that I would add that was just released was the points of consideration that came

out of that C-Path initiative. It was just released on June 12 by Steve Piccoli and John Sauer.

But this, on the left you can see this is the Bio-Analytical Method Validation Guidance that was released. It was draft in 2013. We had a subsequent meeting, a Crystal City meeting, dedicated specifically to biomarkers in 2015. And then the final guidance was then issued. But we do, in fact, have within that document considerations for biomarker assays.

And then there is also a reference from 2005 or 2006, Jean Lee, et al, that talks about specifically how to validate biomarker assays. Some of the considerations you need o take in the analytical parameters, we saw some of them listed by Doctor McShane.

(Slide)

So, I do want to shift gears a little bit here and point to the need for novel biomarkers. So, in the internal medicine space often times subjects will come in at different levels of disease. And they also -- in this particular example, this marker has a parabolic or I should say a log-rhythmic type approach to over time the change in the marker.

So, if you select the animal at a time point, that is then inconsistent you can get results that make it difficult to interpret. And so how do you take then

something that occurs like this and come up with a simple metric that could be used to evaluate progression, in this case of a non-linear process.

You can see from this example, this particular marker was successful at differentiating non-responders and responders. In fact, we did see the cortisol example would be a good one. There it was driven more so by diurnal variation. But this isn't the case where over time the marker is actually progressing up at different rates.

So, one way to address that is this concept called reference change values published by Callum Fraser. But what it takes into account are the different sources of variance, the analytical variance, the within subject variance and then it looks for that change, that delta, in the biomarker to actually signify a medical meaningful change. And then you could use that as a way to define a progression time point.

(Slide)

And so we did that on one of our laboratory studies. And, in fact, we could see, you know, changes in this particular marker over time. It gives us a way to, as I said, take a non-linear process and characterize a progression.

So, again, this is something that we're interested in. We would like to see considered.

(Slide)

So, lastly, how do we determine the evidentiary criteria for evaluating biomarker use. And I thought about this a lot. And I look at this framework and I think it's definitely the approach that needs to be taken. I wouldn't change anything here, which is -- I would start with the context of use box. As I said, each biomarker should have a category and then its proposed use.

And then you need to weigh the risks and benefits in a conversation with the agency. What is the benefits of this marker relative to the risks. And then once you have that conversation you conduct the study. Then you can define that, the actual output of that to determine if, in fact, your marker has met the criteria in order for it to be qualified. So, this again has been outlined by the NIH foundations NIH.

(Slide)

So, this slide comes from, this was just thinking about the entire process of implementing a qualification program or even a companion diagnostic approach. And I did this in collaboration with the AHI group. So, I think Terry will be here to add on.

But I guess a couple of key points that I would like to highlight as far as, you know, there is certainly opportunity here, if you go to the opportunity box for cross

industry collaboration. We heard that today. If you think about it in the human medicine, Alzheimer's Disease has been a great example.

Certainly the biomarker qualification concept should reduce the time to run a study potentially. There should be improvements in animal welfare.

I think the big concerns and threats weaknesses would be around the cost. We also know that we cannot add more costs to the development process or, you know, to the actual patients in the end. So, we need to find a way again to share in this burden across all parties.

(Slide)

So, factors to consider, this is my final slide. I think I am giving a few minutes back. So, that's good.

The biomarker, as I said, must bring value to the patients. Biomarker qualification has to be beneficial to all parties. The timing and body of evidence has to be consistent with the size and speed of animal health trials. Has to promote innovation. Improve the product process. And lastly, we would certainly like to consider the idea of leveraging conditional approval and post-marketing data sharing.

So, with that I will turn over the panel to Phil.

(Applause)

DR. TURFLE: So, I'd just like to invite our

panelists up so we can go ahead and transition.

And I just remind everybody to speak directly into the mike. And so we'll go through the questions and -- so I will start with Mister Katz, and so what are the expectations and as phrased was sponsors, researchers, veterinarians, producers for the use of biomarkers in the context of animal drug regulation and how may biomarkers be use in addition to surrogate endpoint in the design and conduct of clinical studies.

Panel Discussion

MR. KATZ: There is no question that the biomarkers that we heard today have a lot of value to replace some of the very long endpoints, like overall survival. So, the markers themselves have great use in clinical trials.

But where are these markers coming from. And that's one thing that we need to consider is how do you detect these markers. There is a lot of time and investment that needs to be taken to get these markers, to be used both in trials or into care.

And probably the best example if you think back to the NIH trial in 1948 Remington Heart Study. Still ongoing. And they have detected all these biomarkers, like the blood pressures, your lipids, and led to a whole series of papers changing the whole course of treatment for cardiovascular risk factors.

Where do we have to find something like that in veterinary. And that's where -- there is really not that much in veterinary to come up with the same idea. There is a new one with animal -- Mars Animal Foundation that's just now starting to show a single dog breed, Golden Retriever, as representative of all the breeds. What about cats? Fish? Chicken? Goats? None of those will be covered by that one. And that's the first big study.

So, one thing we really need to focus on with that type of question is how do we detect these markers. We don't have an NIH in the veterinary community.

DR. TURFLE: Doctor Ray?

DR. RAY: I think I will pass it on. I covered by thinking on this.

DR. TURFLE: Doctor McShane.

DR. McSHANE: With regard to how we detect the biomarkers, I think you pointed out very well some of the challenges you face in veterinary medicine. The one thing I would say is that when we do collect the biomarkers we need to document carefully how we have collected them. So, how did we measure them, when did we measure them and what was the measurement approach.

So, if we can't do it all prospectively, we need to at least make the best use of data that we already have by carefully documenting it and understanding therefore better

what could be combined.

DR. COETZEE: I think especially in our field where we're working with pain in livestock we obviously have significant animal welfare challenges with that. And as we design our experiments and do these types of studies if we can try to minimize the number of animals that we have enrolled in these types of experiments, this obviously has significant benefits for the animals and for the ethical considerations of the experiment as a whole.

And I think biomarkers play a very important role in that process. Is that if we can develop these biomarkers effectively, I think it not only expedites the approval process but also from an ethical standpoint allows us to address the issue of painful procedures in generating these types of data.

I think the other benefit obviously is being able to find opportunities for researchers and academic environments to be able to interface not only with the regulatory community but also with industry to be able to develop some of the markers that we're working in an academic environment and graduating them, qualifying them to be used in the regulatory process. I think that as supporters is an area that we could work on to be able to more efficiently utilize these types of markers for these experiments.

DR. TURFLE: Thank you. So, I'm going to combine

the second and fourth question. And so, biomarkers are commonly used for diagnosing disease to enroll patients, sample size estimation and pilot proof of concepts studies. So, what information should be provided to the FDA to support their use in these contexts and list some examples, analytic validation, clinical validation and establishing clinical utility or companion diagnostics.

And the fourth question which is very similar is how do we determine the evidentiary criteria so the information that you will provide with the evidentiary criteria to -- that we would use to evaluate these biomarkers.

And so I will start -- Doctor Coetzee, what do you think we should use?

DR. COETZEE: So, one of the tools that we've been a little slow in adopting but have started to use more frequently now as the ROC curves that we talked about today. And we found those to be very useful to really understand what we're measuring. Typically as academics our world revolves around P-values, and so as long as you can get your 0.05 you got a publication, you are good to go.

But I think we've got hundreds of data points, thousands of data points from different experiments that we've collected over the years, that once the paper is published we never look at. And I think that this ROC curve

platform does provide us an opportunity to be able to look at this data in a different way and being able to combine those experiments, a little similar to the meta analysis example that you talked about and collaboration across different researches we can actually really mine a lot more information out of the data that we've collected with these experiments.

Again with that animal welfare consideration, there were a lot of time and effort went into generating these data. There should be opportunities to utilize them more.

So, in response to your question I think ROC curve is something that we're underutilizing, at least in an academic environment on the veterinary side. I've seen very little published on it. And I think that there are some opportunities there for us to make better use of the data we have to be able to inspect these endpoints and biomarkers in a different way.

DR. McSHANE: Yes, I'll just build on that a little bit. I think everything should start with what is your goal with this biomarker, you know, what is the intended use. And then you need to start defining sort of performance characteristics of the biomarker as my colleague here was saying, depending on what you want to use it for. You might have very different requirements about the precision of that measurement, the accuracy in terms of ROC curve or however

you want to quantify it.

And, you know, I find too often people as you mentioned just sort of go after a significant association with the P-value and then you are done, no one looks at it again.

So, we have to have kind of a plan in mind. We have to have an end game. And I think that would really solve a lot of the waste in research if people would figure out where they want to go before they start their study.

DR. RAY: I guess I would follow onto that and say that I agree, that we need to -- you have to understand analytically what you're trying to accomplish, such as what precision number is necessary in order to achieve the type of change that you're interested in.

I did talk a little bit about the concept of serial measures and reference change value, I think that's something that needs to be thought about in terms of when you build these tests, another is index of individuality, these are certainly considerations that need to go in.

One thing that I didn't comment on was companion diagnostics. I do believe that there is an opportunity for companion diagnostics in animal health. As I understand it, there currently is no -- no framework, if you will, similar to what exists in human health. And I think we should certainly consider that for oncology certainly.

MR. KATZ: These assays certainly need to be specific, accurate, everything Lisa mentioned earlier. We also in that same guidance document that's been put out on the evidentiary criteria, they talk about cost effectiveness, tolerability of risk and the value of incremental benefits provided by the true results of the biomarker.

So, we don't want to -- we need to be controlled and validated. Having an assay validated is to show it's a really good assay. Like there is new assay out there for A1C in cats and dogs. The literature questions, it's currently back to diabetes control. So, that needs to be the foundation first.

DR. TURFLE: So, the question three is what are the major challenges in translating potential biomarkers and/or surrogate endpoint into practical tools in clinical trials for animal drugs and what are possibly solutions to these challenges. And I will start back with Mr. Katz.

MR. KATZ: Besides making sure that it is accurate and correlates back to the beginning, you have to make sure that we have common definitions. So, we have cut points, I heard that mentioned earlier. But that's probably one of the weakest areas.

Subclinical mastitis the somatic cell count, but is the cut point 20,000, 300, 500,000? That is probably one of the simplest foundation we need to have standardized so we

know for sure that these markers can be used consistently.

DR. RAY: I think for me coming up with, I guess, a clinical trial process that will allow you to test these effectively. I mentioned that most sites lack the infrastructure necessary to run the study. So, I think putting a lot of effort up front into like I said, lab models and non-interventional studies give you a sense of how stable the markers can be and can they actually be applicable to use in later studies to make assessments on whether you have effected the outcome. That would be my approach.

DR. McSHANE: Yes. Since you posed the question in terms of what are some of the challenges, I think in veterinary medicine certainly the different species and breeds is an enormous challenge. We know even just comparing dogs to cats the same biomarker may have a different interpretation.

So, I think -- I don't have a good answer for that. You know, how you get the funding and other kinds of support and infrastructure to run clinical trials in all these different animal breeds, animal species and even breeds within a species is pretty daunting in my view.

But I do think that we need to -- whatever we can do we have to do the best way possible, which again goes back to making sure that you're using biomarkers that have been -- - biomarker tests that have been analytically validated,

you've done your homework with preclinical studies and, you know, don't jump too quickly into actual studies with, you know, with companion animals for example, before you've done a lot of your homework in other settings.

So, try and understand the biology as best you can. I mean I work in the field of oncology and, you know, nowadays we think of every tumor being unique. So, we almost have the extreme situation of what you have. But there -- you know, many lessons to be learned. That you have to take a very systematic approach and keep, you know, doing the right measurements to understand the biology and combine over studies and look for common themes and that's about all I can suggest.

DR. COETZEE: I think one of our biggest challenges is being controlling variability. I think especially in pain assessment we found very often you'll measure four or five different markers and sometimes they tell you completely different things. And is that a biomarker problem or is that an animal problem or is that sometimes a drug problem. So, I think we've had some challenges really in understanding whether the drug is not working because the biomarker is bad or the drug is genuinely not working.

And so I think we've spent a lot of time trying to figure out the source of variability in biomarker

assessment and very often we discover these things based around the label approval that a company is trying to get if they are looking for labeling in calves, a biomarker may behave very different in six week old calves versus six month old calves. And so understanding that variability and how you deal with those disparate outcomes where you have biomarkers that are telling you different things in the same test system can be really challenging and figuring out ways to do that I think is -- would get us through a major impediment in terms of being able to use these biomarkers in a practical environment.

DR. McSHANE: Could I answer that?

DR. TURFLE: Sure.

DR. McSHANE: Another thing we shouldn't forget, which we are doing a lot in oncology now, is looking at biomarkers signatures. So, it doesn't have to be one biomarker at a time, you know, it may be like in the examples that you were describing, that a constellation of biomarkers where we sort of interpret certain patterns, in the set of biomarkers, will be more informative than trying to look at each one individually and pick a winner.

DR. TURFLE: And then our next question is should the FDA Center for Veterinary Medicine develop a biomarker qualification program like CDER's and would such a program be beneficial. And is it something that stakeholders, such as

drug sponsors, would use. And are there other approaches to the development and acceptance of biomarkers for animal drugs.

DR. COETZEE: Representing the academic environment we wouldn't be directly impacted by this. But I think we could obviously see the benefits of this because from a practical standpoint my colleagues are constrained because they have no drug approvals in food animals in terms of analgesic drugs. They have one drug approved for treating foot rot pain in cattle.

And so I think from a practical prospective we would benefit from having more products available for us to use to manage pain from an animal welfare and a production standpoint. So, bringing that industry prospective from the stakeholders we would certainly welcome that, the development of such a program.

DR. TURFLE: I realize it's --

DR. McSHANE: Yes, whether you call it a formal biomarker qualification program or not, I think it boils down to having people cooperate and bring together the data they have an take a very systematic approach to evaluating the evidence.

And you're right, I mean the academics that I work with, even they don't really understand what qualification is. But they would benefit from at least the

thought process that goes behind qualification.

DR. TURFLE: I didn't know you were giving your opinion on that. Anything?

DR. RAY: No, nothing at this time.

MR. KATZ: In concept qualification makes sense. But right now it has only been I believe eight qualified for human side. And the big ones, lipid panel, c-reactive protein, HER2, cortisol, none of those are on that list. So, there is a lot that still needs to be done on the human side, let alone on the veterinary side.

DR. RAY: I will follow up on that because I looked at that list today, too. Of those eight, six of them were driven by consortia. So, I think that was a point I did make, is that we have to figure out a way to foster animal health consortia. I don't have the solution, but I think we need to figure out a way to do that.

DR. TURFLE: Yes. I would like to follow up since that is one of my later questions, since we've reached the end of the formal questions. I mean, do we have any suggestions on how to wrangle together the various groups to form consortia and --

DR. McSHANE: I mean I think there are some pressing needs you could identify. And one of them is pain, you know. It seems to me you could get together a group of people who all would be very interested in that topic. And

you could sort of circumscribe what set of things you want to deal with. But I'm sure there is a lot of data out there already that could be useful to make some progress.

DR. COETZEE: The National Pork Board is actually driving an initiative like that. It's only been going for a year now, but they have gathered a group of scientists together in conjunction with the Pork Board which is an industry organization to try to validate and identify biomarkers of pain.

And we've had fabulous cooperation from FDA and we really appreciate that in that process. And that's been very beneficial because most of the folks around the table are academics. And we -- understanding what goes into the development process I think has been really beneficial for those of us who work in this field.

And so, that has been a really great example of that and I think within the next year or two we'll have some progress in that area because it is a very pressing need for us in livestock production environment.

MR. KATZ: Certainly this forum brought together academia, industry, government. This is a good type of forum to raise some of those issues and possibly narrow down quite a bit to just a specific topic such as the best criteria, the glossary or the list of sort of endpoints and focus just on that one topic and see if you can come up with a good

collective mind set.

DR. TURFLE: And so, I guess moving on to what I have as the next question. You mentioned asked the framework in the way those questions are outlined and was initially developed certainly for human drug development and research. The Center for Veterinary Medicine has been able to be involved in some of that. But just like feedback if you've been able to look at the definitions there and how well they apply, I guess, as far as veterinary medicine and animal drug development.

MR. KATZ: Some certainly would apply. Still the idea of the rating scales has to be more specific for different species. And having utilization of them. So, right now if one variable is used such as the list of certain endpoints was used once for an approval in any one human environment it's listed. But that doesn't give the industry an idea that if it's used hundreds of times that it's more common, more valuable and possibly a better regulatory effort, and we like to concentrate efforts on those than the ones that were used maybe once.

DR. RAY: I can just comment on the best definitions and how we are using those. We at Zoetis, as I said are not only using the definitions but for each of our programs we give a full detailed plan of how we might address each of those best categories and how they might fit into the

program.

Not all of them are used as I mentioned. The three that were more common were pharmacodynamic enrichment or predictive, excuse me, and monitoring. But I think it certainly can be applied and we are doing it.

DR. TURFLE: Do you have any suggestions for us --

DR. McSHANE: You know, I can only say having been one of the members of that group that developed the glossary, we actually did try very hard to make the definitions broadly applicable. And so we actually want to hear feedback if you feel as though we have gotten too specific to humans.

And, you know, we even had the issue -- we sort of started with drugs in humans. And we said well, wait a minute, there are devices, too, those are medical products. And there is like tobacco products, and there is cosmetics. And there is, you know, all kinds of other things. And then there are animals, veterinary health.

So, we did -- take a very long time discussing some of those definitions. And we hope we have made them pretty broad. But again, we're too close to it at this point, so we need to you from you if you feel as though we're missing the boat on some of those.

DR. TURFLE: And I think this will be our last question. Do you have any suggestions or any thoughts as far as how animal biomarker research has been used for human

pre-clinical drug development, including biomarkers qualified by CDER might be leveraged for animal drug approvals.

DR. COETZEE: I think the comment was made earlier about, you know, leveraging reagents and tool kits we have available of. And mostly in humans and not in animals species. And we've run into that before when we do -- taking cattle work we really struggle to have the reagents to be able to test some of these markers and see if they are consistent across the different species. And so, that's a real deficiency and I think it's something that we really struggle with.

DR. TURFLE: Doctor McShane.

DR. McSHANE: No, I'm just wording since I'm not in veterinary science, you know, for medicine for people we have the NIH. But do you have any other kind of funding organization, the USDA or any other government agency funds this kind of research?

DR. COETZEE: So, the National Institute for Food and Agriculture, which is NIFA, part of the USDA has a funding program that supports this type of research. I think that there are opportunities there for FDA and USDA perhaps to collaborate on some of these specific questions because there certainly would be leverage for both organizations or benefits for both organizations to be involved in that type of program because I think that the end goal is similar and

the stakeholders of both those groups is very similar, as well. So that may be an opportunity.

DR. McSHANE: I mean in the end it gets down to a lot of economics, I mean for all livestock production and things like that. It has an economic impact on us, all of us. It's not just our dogs and cats that we are worried about here.

DR. RAY: When I think of the list of those eight qualified biomarkers maybe the acute kidney injury panel could actually provide benefit in animal health research certainly.

But I think we would have to again go back to the context of use and see -- those have largely been safety driven markers. So, I think -- but I do think it gives us an opening to possibly explore that, that they could be used in companion animals, certainly.

MR. KATZ: When the preclinical is a -- for example, dog, has a question was posed, there is a lot of correlations to human. Question comes up is the disease always going to be the same, like diabetes in a dog, diabetes in a cat, diabetes in human, are they all cross-comparable or is it just good to a dog and not to a cat.

Then one thing you just about touched on, was what about non-mammalians, not just different animals out there. Or four-leggeds, or what about your fish. What about

your poultry. There is no correlation between human per se. That's a whole other area that any type of regulation, any type of an approach needs to encompass those species, as well.

DR. TURFLE: Any other comments before we -- all right.

Well, I thank your panelists. And we'll transition.

(Applause)

DR. TURFLE: And so, I'd like to invite up Kathy Vannatta, who is our -- providing public comment at this time.

Public Comment

Kathy Vannatta

Kindred Bio

MS. VANNATTA: Hello, I am Kathy Vannatta with Kindred Bio. And I am here representing AHI today. AHI appreciates the opportunity to comment on the use of biomarkers and surrogate endpoints, as a tool that can be leveraged to improve the delivery of innovative products to veterinarians, pet owners and producers. Biomarkers and surrogate endpoint have been successfully used in human development space for full approvals or accelerated approvals with the support of post-approval confirmation studies. However, the use of biomarkers in animal health drug

development has been a topic that has been explored for years with minimal meaningful progress.

AHI agreed with CVM that biomarkers are very useful in diagnosing disease to enrolled patients and clinical trials. We also believe there is significant utility to diagnose the presence of subclinical disease such as when clinical signs are not present using somatic cell count for example, to identify subclinical mastitis, or to use biomarkers in a place where endpoints are more difficult to measure or less reliable to measure, such as the use of biomarkers as a replacement for visual analog score or a Likert ordered categorical score that are often prone to either subjective interpretation, bias or placebo effect.

These biomarkers then have the potential to serve as surrogate endpoints that can potentially provide timely evaluation as to the status of the disease of interest.

AHI encourages CVM to also consider how other global regulatory agencies, such as EMA apply the use of diagnostic biomarkers such as vector transmission studies where EMA's guideline references serological, antigen or DNA detection with or without clinical signs present to show the protection and treated groups versus the negative control specifically in lab settings.

To supplement diagnostic biomarkers, AHI advocates that prognostic biomarkers may also a value to *a*

priori forecast and how disease may progress in individuals regardless of treatment in order to stratify patients among treatment arms at enrollment.

Biomarkers can be assayed at baseline, again -- assayed at baseline and again tracked during and after treatment to show that a medical condition has either reached stability or remission or cure after pharmaceutical treatment. And one example of this would be the use of serum and urine M-protein in human multiple myeloma.

AHI definitely understands the need by regulatory agencies for sponsors to be able to justify the selection of a biomarker. There needs to be good scientific evidence from academia or industry that the biomarker is indicative of the underlying condition and that the presence of that biomarker can be reliably detected. Depending on the condition being studied, the presence or absence of the biomarker may be sufficient, while quantitative determination might be preferred to is assay magnitude is correlated to condition severity.

As our industry looks to adopt the approach taken with biomarkers from the human health space into animal health it must be noted that the effort required to validate a biomarker does need to be commensurate and relatively proportionate with our veterinary economies of scale. CVM and the industry will need to collaborate on an approach that

balances between sound science with both the research resources and the population sample sizes.

AHI would suggest that assay validation should not exceed the requirement of existing FDA guidance around bioanalytical method validation. Further analytical requirements on the industry to try to parallel our human colleagues, such as investment and biomarker qualification and regulatory approved companion diagnostics could be challenging, based on the longer development time needed and cost and low expectation of return on investment.

The direct application of CDER's biomarker qualification program to veterinary medicine and to CVM specifically is questionable at this time due to the limited number of successful candidates that have completed the qualification process since its inception. However, as it applies to animal health, uncertainties are still around the cost, the added time to approval and whether collaboration would occur among key stakeholders to contribute to the body of evidence for the needed biomarkers.

One suggestion for CVM would be to consider the use of existing processes, such as the use of public master files or relevant and reliable real world data to support the establishment and validation of biomarkers.

While the human pharmaceutical industry often has dedicated divisions centric to a particular disease, or a

particular condition, with a potential suite of products relying on a common biomarker, the veterinary industry does not always experience the same magnitude of resources or focus on a single therapeutic area. Leveraging biomarkers already validated in the human health space may be helpful for mammalian species, if the disease does have the same etiology, however there is scant research on biomarkers for avian or aquatic species and regulatory requirements may need to be tempered in this instance.

Additionally, acceptance of biomarkers or surrogate endpoints that are generally recognized by veterinary experts or key opinion leaders and are currently used in the diagnosis or management of disease would be beneficial without the need for lengthy justification that may add to the approval time and have additional costs.

In closing, AHI sees much value in progressing approaches that would encourage the application of biomarkers in animal health. Establishment and validation of biomarkers needs to be commensurate and relatively proportionate with our veterinary economies of scale, to be appealing for investment of by sponsors and other stakeholders. If such effort and costs were to be invested, the validated biomarkers needs to be used for primary endpoint assessment.

Finally, we foresee this approach would benefit other drug development areas which could minimize the use of

test subjects, and utilize relevant and reliable real-world data and afford the industry with cutting edge methods that may be able to replace long-standing legacy practices. Thank you.

(Applause)

DR. ELLENBERG: Thank you very much. And at this time we will take a break and resume with the final session at 3:15. Thank you very much.

(Whereupon, a break was taken.)

DR. ELLENBERG: All right, folks. Let's take a seat. And hammer out this last session. All right. Thank you very much.

Topic 4: Foreign Data

Introduction: Ana Lazo, Quality Assurance Study Reviewer

Center for Veterinary Medicine, FDA

MS. LAZO: All right. Good afternoon, everyone. And thank you for being here today. This is the last session of the day today. My name is Ana Lazo and I am a Quality Assurance Study Reviewer in the Office of New Animal Drug Evaluation. And I will presenting on data from foreign countries.

I am joined today by Doctor Mary Jane Ireland, Direct General of the Veterinary Drugs Directorate at Health Canada, Doctor Chase from Schafer Consulting, Doctor Clemence from Dechra Pharmaceuticals, and Doctor Smedley from CFR

Services. Shortly you will be hearing from all.

(Slide)

As you may know there is a rising interest in global development of both drugs and food additives for animal with companies seeking development in multiple countries including the United States. In last year's ADUFA/AGDUFA reauthorization Congress emphasized the important of considering data generated in foreign countries for both new animal drug applications and food additive petitions. So, this session of today's meeting will uniquely consider both.

(Slide)

CVM is seeking input from the public on how foreign data can be used to further support regulatory decisions and your feedback will help us understand your proposed solutions to the challenges faced in using foreign data in US submissions.

(Slide)

In the first question asked we requested feed back on the challenges and potential solutions in meeting the requirements of substantial evidence of effectiveness when using data from foreign countries for animal drugs.

(Slide)

We would like to remind you of the definition of substantial evidence which was applicable to all the sessions

today by paraphrasing, as evidence evaluated by qualified experts to determine if a drug is going to work as indicated. You can find the exact definition in 21 CFR 514.

(Slide)

Question two, in active control studies conducted outside the United States the active control may not be US approved. If the study were submitted to the FDA to support effectiveness it would be difficult for FDA to infer that noninferiority to an unapproved active control demonstrates evidence of effectiveness.

(Slide)

We asked what criteria should be used to accept a study where the active control is not approved in the US What challenges exist in utilizing these studies and what are potential options to enable FDA to use these studies.

(Slide)

Question three, what challenges and potential solutions exist in demonstrating that data from foreign countries were generated under conditions typical of those found in the US for an animal drug or food additive.

(Slide)

Question four, what challenges and possible solutions exist in designing studies that meet the approval requirements of different jurisdictions for an animal drug or food additive.

(Slide)

Question five, what challenges exist in study conduct, collection and interpretability of data that may influence study quality and data integrity to support the approval of an animal drug or food additive. And what are some possible solutions to these challenges.

(Slide)

And finally, question six, what other challenges have you encountered and what potential solutions would you propose with regard to providing data from foreign countries to the FDA.

(Slide)

And now we would like to inform of our participation and efforts with international harmonization and cooperation. We're activity involved in maintaining international collaboration with multiple agencies, such as the FDA EMA Parallel Scientific Advice, the RCC and of course the VICH. In fact, one of our invited speakers today, Doctor Mary Jane Ireland, from Health Canada will be presenting shortly.

(Slide)

We would like to familiarize you with resources available addressing foreign data and international collaboration. Such as the 2012 FDA Safety and Innovation Amendments, which reaffirms that we have been accepting

foreign data for a very long, provided that the data are adequate.

(Slide)

And here are some additional resources including the various VICH Guidelines.

(Slide)

Additionally the ICCF Group in collaboration with the Canadian Food Inspection Agency, the European Commission and Industry Associations published its first two guidance documents earlier this year and are continuing to work on others.

(Slide)

And now I'd like to provide you with examples of animal drugs approved with clinical effectiveness studies conducted outside the US to support substantial evidence of effectiveness. All clinical trials for the approval of all three of these animal drugs were conducted outside the US specifically in the European Union and Australia.

(Slide)

And these are examples of animal drugs where the clinical trials included sites inside the US and in other countries such as the European and Canada.

(Slide)

We would like you to know that the Center's use of foreign data for new animal drug applications and food

additives petitions are very similar in that we have long accepted these data where applicable to support approvals, but are open to feedback about the challenges faced and proposed solutions.

(Slide)

This slide emphasizes that we essentially use the similar criteria for food additive approvals and the questions are the same as we have for animal drugs.

(Slide)

And now I would like to thank you for your time and remind you that your comments are greatly appreciated.

I would like to introduce our first speaker, Doctor Mary Jane Ireland from Health Canada.

(Applause)

Invited Speaker No. 1

Mary Jane Ireland, MSc, DVM, MBA

Director General, Veterinary Drugs Directorate

Health Canada

DR. IRELAND: Thanks very much. Thanks. It is a pleasure to be here today. And I wanted to take a moment to thank my CVM colleagues for the invitation. It really is a privilege to see the common issues that we're all facing as regulators, but also hear the expertise and the speakers they've brought in today. So, thank you very much.

So, I am talking today about the use of data from

foreign countries and really the perspectives of the Veterinary Drug Directorate. For those that don't know, the Veterinary Drug Directorate is the federal regulator for the sale of veterinary drugs in Canada. And veterinary biologics are actually regulated by the Canadian Food Inspection Agency and so I'm really giving the perspective today around veterinary drugs.

(Slide)

So, really two keys parts to my presentation. The first is to explain how VDD uses data generated in other countries in support of regulatory drug submissions.

And then I'm going to switch into something that I feel very strongly about and that the VDD is very focused on, is how we do international regulatory cooperation for veterinary drug submissions. And I'm hoping as I tell this story that you'll see that our approach to the first point enables our experience and our participation in international collaboration and why these two are quite interlinked and why they both help us in terms of challenges and opportunities. So, I'll try to weave that in.

(Slide)

So, I thought you might like to know a little bit about our Canadian context. This is my regulating or regulatory environment and so I have to keep this in mind. Canada represents approximately 2.5 percent of the global

animal health market. And so decisions by companies to enter Canada to file a drug submission as the first point of entry, second or even third, are not based on the size of the market.

Our stakeholders or other stakeholders like animal owners, veterinarians and producers they want the timely access to a very broad range of drug products that they know are available in other countries. International conference attendance, the Internet, all of these tools make it very well known what's approved in different regulatory jurisdictions and in some cases these products help maintain animal health and in other cases they help producers, for example, with their competitiveness.

Manufacturers as they tell me and some of you here today will know more than me on this, but they are looking for the harmonization of data requirements. They don't want to duplicate studies coming into different regulatory authorities and they want administrative processes across the jurisdictions that are -- facilitate the filing of drug submissions and make it easier to bring products to market in multiple jurisdictions.

So, that is what I am mindful of every day and it's certainly what my stakeholders remind us of on almost a weekly basis. It's the timely access to the same drugs and tools that benefit animal health and competitiveness as

competitors in other jurisdictions.

(Slide)

So, to first start on the use of data from foreign countries. I will say that the Veterinary Drugs Directorate accepts data from studies conducted outside of Canada in support of our regulatory drug submissions. It would very challenging for me to find a drug submission that was compiled with Canadian data only. In fact, the majority of the submissions would probably look like entirely US or EU generated data. And some would be a compilation of a few clinical trials conducted in Canada.

So, we see many of them coming from the United States and the European Union in our dossiers.

We clarify our position, Health Canada's position for our industry members around what is required in terms of data and in the preparation for veterinary new drugs submission guidance we say that it must meet the standard of Canadian conditions of use.

We ask ourselves with every dossier, with every evaluation, particularly when it's foreign data, will it be efficacious and will it be safe for use in Canada in Canadian conditions.

(Slide)

If the data is originating from a study conducted outside of Canada the onus is on the manufacturer, the drug

manufacturer to demonstrate that these studies were conducted under conditions similar to those found in Canada and really answer the question the regulator has, is will the drug perform, will it be safe and will it be efficacious in Canada.

(Slide)

So, unapproved comparator products, and I notice we added this because it was one of the questions, we will accept unapproved comparator products as controls, positive controls in regulatory trials, but we accept those on a case by case basis. And there are many factors that we consider and the evaluators consider when they look at that data.

The sponsor may need to bridge if we have questions about what the molecule is, what the ingredient is, do we have any familiarity with something similar in Canada, it's the sponsor's responsibility to answer those questions and to bridge the information so that we're comfortable with that particular positive control.

It also helps when the positive control has been approved by a trusted regulator. So, the European Medicines Agency, the Center for Veterinary Medicine, the APVMA of Australia, the New Zealand regulators, we know those regulators, we know that the studies were conduct in their jurisdictions, we know there is oversight and so that helps in the decision that we take around positive control in the

drug product that was used.

(Slide)

So, when we think about will the product work in Canada there are times that we may ask for additional information. I would say that we don't often ask for Canadian made studies, but the companies do have to answer questions around, will the pathogen, is the parasite strain similar to those or similar enough to those that are found in Canada. The animal husbandry practices vary across the world and are they similar, those studies that were conducted, do they reflect the Canadian husbandry practices for dairy or pork or for beef. And so it's a really important question that companies will have to address as they file their dossier.

There are genetic differences that we need to keep in mind, and again companies will have to address that in their filing.

We have climate issues. It's cold in Canada. And so when we think about teat dips, which we regulate, we need to make sure that we're taking into consideration the humidity, the very cold temperatures. They're not the same as in Florida. When we think about Calgary and Alberta in the wintertime. So we really need to reflect on that and make sure that we're taking those products and those factors into consideration.

(Slide)

The other area where we use information that helps bridge, it helps fill gaps, it helps inform the evaluators is the use of post-market data for pre-market submissions. So, if the product has been approved someplace else, by a trusted regulator, we will extensively look at the post-market information coming from those jurisdictions to make sure we've got it right. To make sure the labeling if it's approved is right. And to make sure that if we use the information we have to fill gaps. And it's a lot like real world evidence.

(Slide)

It is not without its challenges, using data from foreign countries but we jump those challenges, we jump that hurdle. But it's work for us. Data integrity varies between countries. And it is hard to verify sometimes whether the clinical trials were properly conducted. But when they're conducted in countries for which we have a regulator that we know and we know the system we have more confidence in those trials.

For example, in the US there was regulatory oversight and the CVM is obviously a trusted regulator.

(Slide)

The other challenge we face is that we have limited ability to participate in study design. If the

companies have already compiled the dossier, the studies have been done, we have not had the opportunity as a regulator to input on things that we think are missing, too make comments on the positive control that might be selected and so that's often a challenge when we see a dossier filed after it's been complied, the research has been completed because we have to work through those challenges and often that's a lengthy exercise and it's a lot of work for both the regulator and the company sometimes.

(Slide)

Meeting the Canadian geographic conditions and explaining the antiparasitics, antibiotics and climate, there is a lot of back and forthing that has to go on with companies. There are scientific rationales that have be compiled. There are justifications. There are expert opinions. There are different ways to compile that information and we have to do those from time to time on a case by case basis.

(Slide)

When we do things on a case by case basis we introduce the possibility of not being consistent. And that's important as a regulator. We need to be predicable. And we don't want variation amongst reviewers. So, that case by case is not optimal. But that is sometimes the reality of a regulatory review of foreign data.

(Slide)

So, the data requirements as I mentioned before, when it's filed in a complete dossier, if we have questions, if we had concerns on the trial design, if we had questions on the positive control or if we had been able to influence the sites of the clinical trials to the bordering states, for example, in the United States, it's beneficial for us and it cuts out some of the back and forthing with the companies and having to fill gaps in other ways. So, those are our challenges.

(Slide)

So, I wanted to switch into international regulatory cooperation. And I would say that the space that I'm about to talk about is really enabled because of our use of foreign data.

(Slide)

So, we are currently conducting reviews of veterinary drug submissions with different various regulatory partners across the world. The first is a simultaneous review with the United States Food and Drug Administration Center for Veterinary Medicine. The second is joint reviews with the Australia Pesticide and Veterinary Medicines Authority and the New Zealand Ministry of Primary Industries. And the third is an opportunity for joint or simultaneous reviews of which we have just engaged with, with the UK

Veterinary Medicine Structure and I'll go through each of these models.

(Slide)

So, first the simultaneous review with the CVM it's under the umbrella of the Regulatory Cooperation Council Initiative. We accept submissions being filed for new drug submissions, supplements and we have recently opened this up further to include genetics.

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So, the premise of this model is that a company files the same submission, the data sets are the same at the same time to both regulators. And so you can see here if the data is coming into the CVM and we are accepting the same data really we're in a better position of we can use the data without having to have add-ons by the company. So, without particular issues having to be addressed with a Canadian study. Or additional justification. Or scientific opinion.

So, the premise is that we are largely, almost exclusively, taking the data that is being filed to the CVM and we are reviewing that at the same time. It's an independent review. The reviewers are discussing their findings with each other. And it is done in parallel and independently. And we make independent decisions.

(Slide)

And to date we've had eleven veterinary drugs

approved under this pathway and seventeen others have been accepted for review or ongoing under review. And so this has been a key, key factor of achieving the second point that I stated out in the Canadian context. Simultaneous access to drugs by our producers, veterinarians, animal owners, is facilitated by this particular model with the CVM in North America and the premise of this is accepting the same data set with very few differences.

(Slide)

We're also conducting joint reviews with Austria and New Zealand, the regulators there. And in that particular model the sponsor files a submission with all countries simultaneously. Again, to the extent it can be the same data, it should be the same data. The work is shared in this particular model so each regulator leads a particular set of review on efficacy, safety, product management is shared as well. And then the second reviews are done independently by the regulators themselves. And again the reviewers discuss their findings and we risk manage usually in a similar way.

(Slide)

So, the assessments are used by the regulators as the basis for independent regulatory decision making. And we've completed one review and we have two underway.

And again, the use of foreign data factors

largely into this model. Studies done in Australia and New Zealand, if it makes sense for us to accept them in Canada as a regulator, we will endeavor to do that.

(Slide)

So, international collaboration is possible for us because the regulators that are involved in this space have a willingness to see commonalities in regulatory systems and to learn by doing. And this I would say is a group of like-minded regulators.

We have harmonized technical requirements established through VICH and we have food safety standards that are quite harmonized under CODEX. And again as I've mentioned a few times now, the acceptance whenever possible of data generated in other countries and avoiding the need to duplicate studies makes international collaboration and companies willing to participate in these models possible.

(Slide)

There is ongoing exchange of scientific information and all of the regulators that I have mentioned are very forthright in that and we share review reports and discussions between evaluators to risk mitigate and to ultimately approve these products, we have done eleven times.

(Slide)

We have systems in place to product confidential information which is provided by sponsors and these are

memorandums of understanding between the regulators.

So, that is what makes international collaboration possible for us and for me to achieve objectives of the expectations of our stakeholders, which is the timely access to safe and effective drugs in Canada.

(Slide)

So, that is the story of both using foreign data as it relates to the Veterinary Drug Directorate, and international regulatory cooperation.

I would just say before I close that some of the challenges I highlighted earlier in the presentation around the use of foreign data are actually resolved when we work together.

First of all when we conduct Regulatory Cooperation Council simultaneous reviews with the CVM we often get engaged by the companies early on, when they are developing their clinical trial protocols. And so, when we receive a dossier at the end of the day that is already formulated and has used a control that we don't know very much about, that is eliminated by upstream activity on our part in helping to design the clinical trial, which occurs when we conduct in regulatory cooperation. So, many of those challenges actually get ironed out when we work together as regulators and we work together early.

And so I hope it's helpful as I explained our use

of foreign information. I would reiterate that in many cases this is done on a case by case basis but with effort and collaboration and coordination and communication with companies, we can quite often achieve really a win/win solution. So, thanks very much for your attention today.

(Applause)

MS. LAZO: Thank you, Doctor Ireland. Now, I'd like to invite our next speaker, Doctor Sharon Chase from Schafer Veterinary Consultants.

Invited Speaker No. 2

Sharon Chase, DVM, MPH

Schafer Veterinary Consultants, LLC

DR. CHASE: Hello. It's good to see some faces from before. I'm Sharon Chase. I'm trained as a small animal vet. I also have background in public health. And I worked at CVM for a number of years. And now I currently work for Schafer Consultants, based in Fort Collins, Colorado. So, I've been told that I am a little bit soft spoken. So, I'm going to -- anyways I am very excited to be here today. So, thanks very much for the opportunity to be here.

(Slide)

So, I'm just going to go through each question one by one with some examples and then some challenges and then some solutions.

(Slide)

So, first question, and an example that we see very often foreign CROs may have FDA experience but not CVM experience per se. On the other hand they may have EMA experience, but not have worked with the FDA in the past at all.

So, the challenge is it's sometimes hard for firms to understand why CVM is not the same as other branches of the FDA and why it's not the same as the EMA. So, how can we find a solution.

(Slide)

So, one idea is to prepare a high level document that compares and contrasts requirements between CVM and CDER, for example. Another option is to consider an on-line course with the EMA and also amend this to add in Canada, to talk about the different requirements. And I really feel that increased awareness and just talking through this would lead to much better outcomes and less frustration for all sides. And ideally would also lead to more approved veterinary products. Which is all of our goals.

(Slide)

More solutions. Work with the EMA to create a guidance that outlines what's different and what's similar between the two bodies approval processes. And this is something that I'd also like to propose to create a seminar

in that industry.

And so for an example, just this past Spring, CDER and CDRH held a seminar in Boston. And the conference was basically a hands on opportunity for people to meet with individuals from the FDA, to talk about how to file with the FDA, how to get drugs approved with the FDA and at the end of the day there was an opportunity for questions. So, that would immensely helpful for industry.

(Slide)

Question number two, so, in a perfect world firms would contact CVM or the EMA or Canada before they actually run their pivotal studies to ensure compliance between their agencies. But unfortunately this is often not the case. So, looking backwards how can we solve this problem.

So, one path forward is to consider combining the results of an non-inferiority study evaluating an unapproved comparator, with a smaller, shorter duration US field study using an acceptable active comparator. And these two studies together could provide substantial evidence of effectiveness.

I just want to add the caveat here that this could be impacted by the length of time, the unapproved active has been on the market with the EMA as well as any US field experience with the unapproved active comparator, either positive or negative. And then the incident of types of adverse events or AEs, reported for both the IVP and the

comparitors in the PSURs as reported to the EMA.

(Slide)

Some more ideas, if the study was well powered and it was run using a valid protocol you could consider evaluating the results with published literature, any pilot studies that you have available and then run a small US based study and then take all that data and then run either a systematic review or if it's appropriate based on the stats run a meta analysis. And this could provide a reliable estimate of the IVP's expected effect in the field.

(Slide)

Question number three. So, the challenge that we see often is in order for foreign study results to be applicable for US approval and to limit bias as much as possible, there should be confidence that the study populations are comparable.

So, one solution is sponsors can provide a background like a white paper that lists the basically main points of the animal health industry and their respective country. And so, this could be things like animal demographic. What is the estimated county-wide species population. What are the typical living conditions and husbandry practices for this species.

For companion animals, for example, do they live outside with owners or outside in kennels. What is the

average expenditure by owners for vet care. And if known, what is the number of cases seen each year in each species.

(Slide)

CVM question four. So, the challenge that we see at Schafer, we have clinical team, as well, and they often see that field studies designed to meet EMA requirements need to include ABON coding, which is a causality assessment for adverse events. And of course this is not required by CVM. But this adds a lot of additional time and training need to achieve compliance in the field.

And AE reporting to CVM is often very hard for foreign sponsors to understand, why is it not the same, why are there these differences.

And so, possible solutions, well of course the ABON is a EMA requirement. So, there is no going around this. This is for companies that want to pursue approval by both the EMA and the FDA, this is a requirement. So, the best solution might be increased awareness of how the EMA and CVM is different in terms of requirements for reporting field study AEs.

And this going back to my first slide, the first couple of slides, this can be accomplished through webinar training and preparing a white paper that shows the requirements for AE reporting, for EMA and CVM.

(Slide)

Question number five. So, one example foreign firms and also US based smaller companies may not have previously done file conversion from Excel and Access to XPT or XML which is required for eSubmitter, trying to process eSubmitter submissions to CVM. And so the challenge is fairly straight forward to explain how to convert one or two small files, but trying to helping someone to covert an entire data set, especially if it is an EDC from a large field study, is very time consuming and there is the risk of errors in this process.

(Slide)

So, one way to move forward on this is to provide step by step instructions on how to convert files. So, ideally this would be done in English, of course, but also in other languages spoken by foreign firms, such as French, Spanish, Chinese, and Japanese. And this information could be shared in a Webinar or on the CVM webpage.

Another tool could be to use project managers to provide general assistance with helping firms understand what files are needed from EDC studies and how to gather that information would be a huge benefit to industry.

(Slide)

Another challenge, use of scientific notation and foreign data is inconsistent sometimes with US practices. For example, the use of a comma instead of a decimal point

could lead to significant errors during a file conversion. And I have an exclamation point here because this strikes fear in my heart when I see this on a data set. But the great news is that it's pretty straight forward to fix this moving forward.

Foreign sponsors should ensure that data used to fill CVM requirements should use a decimal point and other scientific notation as appropriate.

(Slide)

Another challenge, foreign sites may not provide a reference range for blood work obtained in field studies. And this might make it challenging to interpret individual results and trends from field studies.

So, some solutions, sponsors should attempt to use foreign labs that have species specitific relevant reference ranges. But if these are not available this sponsor can consider providing additional stats to help interpret their results. And this includes things like frequency distributions, histograms and combined presentation of individual animal data over all time points from a field study.

(Slide)

And CVM question six. So, the challenge is, requirements are sometimes challenging to understand by those whose first language is not English. And so one straight-

forward solution would be to provide translated copies of frequently referenced guidances. And of course, there is a cost with this. But the cost for translation is likely minimal compared to the cost associated with failed submissions and the need to repeat studies.

And that's all I had today. I would just like to say thank you very much for this opportunity.

(Applause)

MS. LAZO: Thank you, Doctor Chase. And now I'd like to invite out next speaker, Doctor Richard Clemence from Dechra Pharmaceuticals.

Invited Speaker No. 3

Richard Clemence, BSc, MSc, Ph.D., MBiol MRQA

Dechra Pharmaceuticals

DR. CLEMENCE: Thank you very much. Good afternoon, everybody. My name is Richard Clemence, I work for Dechra Pharmaceuticals as the head of Global Clinical.

Firstly of all I would like to thank CVM for the opportunity to come and speak here today. And secondly thank both my colleagues and friends in Dechra but also in the wider animal industry for their opinions, comments and real life stories that they've contributed to what I am about to say today. Sorry, pressing the wrong button. I went for the obvious arrow.

(Slide)

I'm not going to go through the list of questions, you've seen them several times. I'm also not going to answer them question by question. But I hope by the end of my presentation you've got a flavor of my thoughts on each of the six questions that were asked of us as speakers.

(Slide)

In thinking about how to address these six questions some headlines or key assumptions, I think, that came to mind. First of all, I think it's important to state up front that CVM and industry we share two common goals in this regard. One is the licensing of new safe and effective veterinary medicines. And the other one is what we heard this morning is support for animal welfare in terms of animal testing and the requirements for registration of those veterinary medicines, the refinement, reduction and replacement of animals where possible.

I think we would also well recognize that the costs of both studies and development programs as a whole are rising, inevitably has an impact on what products do and don't get registered.

Although today we are talking about the challenges of getting foreign studies accepted by CVM, substantial evidence, we should all remember and it's been clearly stated, they are already clearly stated as an accepted data source within the regulations.

The challenge from an industry perspective, I believe, is that what is and not acceptable is often difficult to discern. And without clear guidance companies often revert to doing stand alone studies in all of the geographies in which they're seeking registrations or a large majority of them, rather than at the very least trying to combine data sets to reduce animal numbers and costs.

(Slide)

So, two open questions. Can CVM provide more specific guidance to industry. And are there already ways to allow more foreign studies to be considered than are currently being fully utilized.

(Slide)

So, when we consider submitting foreign data or data from foreign studies, I think there are two clearly very different situations. There is the planned study versus the already completed foreign study. Clearly in a prospective or future study this offers the opportunity for the sponsor or the animal health company to have an up front conversation with the agency to insure that the data to be generated will provide substantial evidence to support a US submission. And the obvious way of doing that is to obtain protocol concurrence. That's the optimal way to try to insure future acceptance of the study.

But as we all recognize for both parties it has a

time and a cost consequence. And if the intention also to submit that study in another country, normally the one in which you are conducting the study, then there may be competing requirements from that agency.

Well, as Doctor Lazo pointed out right at the beginning, there is already a mechanism, and I would like to come back to it later, which -- for certainly between the EU and EMA -- EMA and CVM of obtaining parallel scientific advice. And as we've also heard from Doctor Ireland, there are also other ways whereby the regulators collaborate. I'll come back to that.

Obviously a compromise to seeking protocol concurrence is simply to meet with the agency or communicate with the agency to discuss plans and align on key features.

And more specifically, if you're using an active control in a firm study, try to use one which is already licensed in the US if feasible. Dechra has previously done that way before my time, so I'm not claiming any credit here. But there was no suitable license positive control in the country in which they wished to conduct the study and therefore they sought a license to import the unlicensed active control, in this case to France, ran the study against the IVP, successfully got registration.

The alternative as we've heard from some of the other speakers is to design and conduct a foreign study and

the US study to a common or a very similar protocol to enable a cross-trial analysis to be conducted retrospectively.

Obviously, if your foreign is already completed, you have far less flexibility. If the product under test is already licensed and used in other countries and if your study is well run, well controlled, with strong statistical evidence of efficacy against appropriate control, can it be supported by real world evidence. We've heard a lot about real world evidence in a preceding session today.

And will it therefore provide a total package sufficient for a full approval in the US of the desired claims or perhaps for a conditional license.

(Slide)

So in thinking about the different types of data, that a sponsor might have, I drew up this very simple decision tree trying to illustrate the options, the colored boxes on the slide are intended to increase -- to indicate the increasing degree of risk when considering your foreign study. So, I am moving from green to amber to red.

I would assert generally safety data is always admissible.

If we look here at the -- when I first drew this diagram, I had a lot more levels to it. Before I got down to the conduct a gap analysis. So, for a completed study for example I would suggest -- and it was eluded to in some of

the earlier presentations -- whether you've conducted that study in a region that is a signatory to the VICH, for example Europe or Japan. That might increase the credibility of the study. It's likely to increase the rigor with which you've probably done the study and the data set you've compiled.

You may indeed have done the study in a country where study sites are inspected, Denmark would be an example in the European Union. That again reduces the risk. But nevertheless, whether it's a completed study or the other options over there, at some stage you're going to have to conduct a gap analysis compared to the regulations in the country where you were doing the study versus those required for CVM submission. And try and bridge any gaps.

(Slide)

So, it says at the bottom right of this slide, this is not a complete list. It's just intended to highlight some of the key areas. I notice people laughing, maybe it is a complete list.

(Laughter)

DR. CLEMENCE: But I wouldn't be bold enough to say it is. But it's intended to highlight some of the key areas for consideration when determining inferential value of foreign study for US submission. And I'm just going to highlight a few of the points here.

Clearly whether or not the exact same product has been used in the foreign study, as you intend to try and register in the US is key. Without this the study is highly unlikely to provide any substantial evidence. I think that's self-evident. Sorry.

If the product is already licensed or the product and the test is already licensed in the US for another indication, it's obviously going to be much easier for CVM to interpret the value of any foreign data for new indication or new species.

The age of the data to be presented, that's clearly important, but the older the data the lower the likely inferential value to any regulatory agency.

And the sponsor's ability to submit raw data, for example patients and owner details, will come back to this on a subsequent slide, but one marked difference sponsors observed between different agencies is the type and amount of information that's required to be submitted as raw data.

The use of real world evidence of safety and effectiveness. And I would suggest this is an area where the agency and industry can work together to improve the routine acceptance and value of such data and indeed we've heard a lot about that earlier.

(Slide)

So, can we categorize studies as to their higher

or lower inferential value. Some studies to determine the effectiveness and safety of medicines for some disease indications in some animal species may be more globally applicable and relevant as evidence of effectiveness than others.

For example, pain, cancer, neurological and metabolic conditions in diseases are probably less influenced by extrinsic factors, such as climate, husbandry or production system than infectious diseases. And for many of those conditions or diseases they are of course significantly linked to intrinsic factors such as genotype, age, sex, reproductive status, et cetera. But with detailed information on the patient population recruited in the foreign country, on the husbandry of the animal before and during the study, I think the inferential value can often be maintained.

Of course if the disease pathogenesis is significantly effected by climate and husbandry than the inferential value of the study done outside the US may be lower to the US. But of course, climate and husbandry do vary widely across the US, so such data may have relevance for the US, also.

And I did try and thing if there are any foreign studies that have no inferential value at all to a US submission. In my opinion the answer is clearly no, all

studies are of value if well conducted. At a minimum in supporting the safety of the product under investigation and they can, of course, provide inferential value on effectiveness.

(Slide)

So, challenges with -- sorry -- what are the major challenges to acceptance of foreign data. And I tried to highlight five here. So, study design differences, differences in interpretation of VICH, GCPV, submission of raw data, evidence of data integrity and differences in study masking requirements.

If we come back to study design, for example, the US preference to have placebo controlled studies where possible. And I would suggest the mitigation is to discuss any differences in study design or if conducting several studies across more than one country, a foreign country for example and the US, use the same or similar design as possible.

Clearly for some indications that's easy. Motion sickness in dogs or cats, but for more complex diseases situations such as bacterial infections in cattle, it may be much more challenging.

Differences in interpretation of the VICH, GCP, this I think is often the most challenging for sponsors to predict and avoid. And mitigation, I just wonder whether CVM

could provide a checklist of expectations based on observations of issues from previous submissions.

Submission of raw data. I think there are two challenges here. Different agencies have different views on what is and is not raw data. And secondly, unlike the US many countries don't currently require the submission of raw data. Although it should be noted that the number of sponsors do routinely submit raw data with their authorization applications in other countries.

Many sponsors, I have heard sites data protection laws, particularly in Europe, is reasons why it is difficult to submit raw data. I don't actually believe that with good planning that is reason why you can't submit raw data. Under the European data protection laws, provided you obtain informed consent up front data can be submitted under certain circumstances. And they're not too restrictive.

Evidence of data integrity. This is what all sponsors strive for, for all studies, but there are differences in what is considered sufficient evidence. Just one simple example I would give you is when conducting a field study in a non-English speaking country, I would always suggest doing it in the native language, for the simple reason is that you can provide a translation of the raw data and if the translation is considered inaccurate you can repeat it. However, if the investigator didn't understand

the question on the English data capture from the first place, there is no way you can replace that data.

And finally, differences in study masking requirements. This is not US specific but it does often seem CVM take the toughest line here. Masking requirements do need to be practical and workable as well as fit for purpose.

(Slide)

So, foreign studies may not -- sorry -- foreign studies may use an active control not used in the US. The simplest solution to this issue is obviously if the foreign -- - if the sponsor has a choice of active controls for foreign studies, choose one that is already licensed in the US or if feasible, as I was illustrating earlier, import one. But we all know that's often not possible. The more complex but usual option is to use a locally licensed product as the active control in the foreign study.

I think in this situation you have two choices and they're not mutually exclusive, one is to run a foreign study and the US study to a similar protocol as possible and enable a cross-trial analysis and keep the animal numbers to a minimum across the two studies. And the second one, certainly within the foreign study but also in the US study, is capture as much additional evidential data as possible particularly on the foreign study to demonstrate the applicability and efficacy of the IVP to he US population at

large. And provide as much additional evidence as possible to demonstrate the validity of the study and the data generated irrespective of that active control.

(Slide)

And in closing I'd just like to suggest two other ideas. Actually one of which was touched in Doctor Lazo's opening comments here. For sponsors when conducting certainly EU and US programs and we've heard from Doctor Ireland information about other collaborations between regulators, but consider use of the parallel scientific procedure process between the US and Europe. And for CVM consider broadening the use of conditional approvals to include products already as registered in other major markets when supported by real world data.

So, the parallel scientific advice process, it enables the company as we've heard to received unified advice from FDA and EMA, has been available for over ten years and it seems to me that it's more widely used on the human side. And I detect amongst the animal health companies just on a straw poll that there are still concerns that seeking advice via this route may result in a company needing to design a development program of study to meet the higher of the two standards. There is almost a fear of a bidding war between the two agencies.

Rather than as was intended when the process was

set up, the two agencies coming together to reach consensus. I don't believe that's actually the reality and according to one global CRO that I spoke to, which has conducted a large number of these parallel scientific processes and indeed at one stage had done the majority of them, they looked back and did some analysis and in all cases they were able to say, that compared to the existing programs that they were proposing for Europe and North America, following parallel scientific advice, the overall program was reduced in size and cost to the benefit of the sponsor.

So, I think it's an underused process by the industry in terms of veterinary medicine registrations.

The current US conditional approvals process as I understand it is designed to encourage the development of products for MUMS, unmet or difficult indications. I would propose that CVM considers broadening this to include US registration of some products already registered in other countries which CVM considers to have a robust regulatory process when supported by real world evidence.

(Slide)

So, in conclusion, I do recognize and I think we all recognize that one size doesn't fit all when considering foreign data as part of the US submissions. But as we all know, foreign data are an accepted study type. And I think that we, the industry and the regulators need to work

together to try to leverage foreign data, whether it be for US submissions of all US data for European submissions or Canadian submissions or whereever, wherever possible to try to reduce animal testing and speed the flow of safe and effective veterinary medicines to market.

And the two potential opportunities I would leave you with would be CVM broadening conditional approvals and industry, at the very least, looking at the parallel scientific advice process more closely. Thank you very much.

(Applause)

MS. LAZO: Thank you, Doctor Clemence. And now I'd like to invite Doctor Kristi Smedly from CFR Services.

Invited Speaker No. 4

Kristi Smedley, Ph.D.

CFR Services, Inc.

DR. SMEDLEY: Thank you very much for inviting me today. I am a unique person as many of you know, I am your only feed person talking today. So, I've taken this opportunity to provide some additional information so maybe you will understand some of the unique areas that we have in feed ingredients.

(Slide)

So, the FDA Division of Animal Feeds is the group that looks at animal feed submissions. And lots of times when I try to explain who the Division of Animal Feeds is,

it's like take all of ONADE, shrink them down significantly and have them look at animal feed ingredients and that's pretty much what it is.

They look at three different types of submissions, food additive petitions, animal GRAS notices and requests for AAFCO definitions. These submissions generally cover manufacturing information, utility, which you guys pretty much know as efficacy, target animal safety, human food safety and environmental safety. These are the same areas that we review for animal feed. I mean animal drugs, also.

(Slide)

Data requirements vary significantly based on the ingredient, the submission type and the available public and published data. In some cases specific safety or utility studies, which are often times conducted under GLPs and GCPs are required and others a white paper assessment of available data is satisfactory.

Data from studies conducted in foreign countries in many circumstances may support FDA feed submissions, either as stated -- other as the specific studies or in support of the white paper assessment.

(Slide)

And as was said by the previous speaker and I'm sure many other speakers today, generally safety studies

conducted in accord with GLP or OECD guidances are found acceptable to support a feed ingredient submission. There is always caveats to this, but that is a general statement.

Often times FDA will request a GLP statement identifying how the study does not meet GLP requirements if the study was not conducted and that can sometimes be -- difficult for our feed ingredient manufacturers to provide, but it is one way of meeting this requirement.

(Slide)

It's far less likely that the Division of Animal Feeds will accept foreign studies to support the utility or the efficacy studies required to support a feed ingredient submission. This is for a number of reasons. And I will go through some of those reasons.

(Slide)

The Division of Animal Feeds generally requires these studies to be conducted using typical US feeds, corn/soy diets and also they frown upon the fact that if they use any other ingredient that's not already listed or authorized for use in the United States. So, perhaps vitamins or minerals that are used in the country of that you are doing the study in, they may not be authorized in the United States. And sometimes other ingredients are in the feed. And they are also interested in using animal stock generally similar to those found in the United States.

(Slide)

Often foreign studies pivotal parameters are not consistent with the Center's policy for acceptable claims for feeds. Which are found in the Policy and Procedure Guide 1240.3605.

(Slide)

The European Union, Canada, Brazil, Japan, China and many other regulatory jurisdictions permit data demonstrating that feed ingredients can maximize animal production. Feed efficiency and average daily gain to support the utility of new feed ingredient. And this is a very typical way of demonstrating utility in these jurisdictions.

The Center for Veterinary Medicine does not permit the use of animal production parameters to support what would be the pivotal parameter for feed ingredients.

I'll go on and you'll see later in my presentation that I would suggest that this is contrary to the Federal Food Drug and Cosmetic Act. But that is their policy currently.

There are other jurisdictional differences and other parameters that are not permitted to support utility of animal feed ingredients. And I know that even in Canada there are some things that are permitted in the US that Canada doesn't permit. So, there is not, as far as efficacy

or utility, there is not this consistency that would be helpful for the feed industry.

(Slide)

I went through a few of the questions that were germane to feed ingredients, as I was asked. And this was one of the questions about whether or not there was -- I provided a solution and so or I suggest a solution.

If a full study report is available generally the conditions are provided so we can demonstrate that the conditions that are used are similar to the US. However, published studies, which we often rely on in feed ingredients do not have that detail. So, it's very difficult to demonstrate whether or not these conditions are equivalent.

If the investigator is not available to provide a compliance statement that also can sometimes result in an unusable study.

Foreign translations of scientific terms, may also result in unusable data. And we had a very good discussion about how sometimes just the record keeping is -- would suggest that the data can't be useable.

A solution that I'd like to offer or suggest is being that what these products are, they're feed ingredients, they're meeting the nutrition of the animal, or they're providing technical ingredients, how important is meeting US conditions on the measured parameters and have we perhaps

gone a little too far with that whole idea that a feed that includes wheat as a major ingredient is so substantially different from a corn/soy type diet.

(Slide)

Another question that was posed by CVM, and my suggestion is the significant challenge for utility studies to select and validate pivotal parameters to demonstrate utility or effectiveness in multiple jurisdictions.

These -- this industry is small, it's a very small industry. And to try to run a study efficiently and effectively that would be acceptable across a number of jurisdictions where there are small nuances between every pivotal parameter makes it really difficult to be effective and efficient in using animals and the other resources that are available.

And as others have suggested we are doing -- we're just now beginning to do some VICH type guidances between the different regulatory agencies, but there needs to be both some -- these guidances are important. But we also need some better discussion in-house as to what is and what is not acceptable.

(Slide)

And as I alluded to earlier, specifically for utility studies the Center should revoke the working policy of the use of animal production -- which prohibits the use of

animal production parameters, as it is contrary to the Federal Food Drug and Cosmetic Act, 301(g)(1)(c), which specifically states food may affect the structure and function of animals. This would permit the broader use of cross jurisdictional utility studies.

And if there is one thing that I would like to renumerate* here is this is so important. We are using animals inefficiently. We are not effectively able to do this because of a policy that was made in 1998. And I think it's time that CVM goes back and reconsiders this policy.

(Slide)

So, what other challenges exist in the study conduct and the collection and interpretation of foreign data. We have minor differences in study conduct requirements, minor differences in experimental designs, minor differences in statistical interpretation of the data. When the raw data package is available you can ameliorate this but it makes it very difficult. And I think some of this can be -- one solution is to have a more accurate understanding of the impact of feed matrixes on the parameters that we are assaying for feed ingredients. Which are not drug like parameters. These are feed parameters that look at just nutrition and they -- and the nutritional value of the feed.

(Slide)

And the last question was, what other challenges have you encountered and -- the challenge that chose to describe there is the division scientist are typically more comfortable in accepting data from US scientists. They especially like investigators that they are -- that are known to the reviewers. And I understand that. I have been a reviewer at the Center for Veterinary Medicine in the Division. But it's time for us to be outside of that box.

It's necessary for the Division to be more cognizant of the financial and the animal costs of additional studies when adequate data is available from foreign sources.

It's also important for these feed ingredients to understand we now have a very sophisticated animal industry. There is a real question as to the need for this level of efficacy or utility data when there is not a single large animal producer out there that will accept a new product without testing it in their own system. And that's just what's understood and that's what's the current status of the animal industry.

So, I think it's time for the industry to meet with and discuss these changes with the Division and come out with a workable solution that assures the safety and utility of all feed ingredients, but does not need to go that N-th degree. Thank you for your time.

(Applause)

MS. LAZO: Thank you, Doctor Smedly. And now we're going to take public comments. And I believe we have one person, Nikki Phillips.

Public Comment

Nikki Phillips, VMD

Elanco Animal Health

DR. PHILLIPS: I'm Nikki Phillips with Elanco speaking on behalf of AHI. Registration in the United States for animal health products that have been previously approved and marketed in non-US geographies usually requires relatively extensive development programs despite the availability of foreign data. This may unnecessarily increase animal use, hinder the speed of registration and ultimately reduce the timely access of therapeutic options available to veterinarians and animal owners in the U.S.

This public meeting is timely as AHI sees opportunities to facilitate the use of foreign data without negatively affecting the quality, safety or effectiveness of animal health products.

There are two main challenges AHI members would like to highlight regarding the use of foreign data from previously conducted studies for CVM submissions.

The first challenge is that the lack of protocol concurrence prior to study conduct often leaves the sponsor vulnerable to the determination that the study design is

considered to be inadequate or insufficient by the CVM to support certain claims. For instance, in the EU, it is common to conduct studies against a positive control to demonstrate non-inferiority. In the US however, studies to demonstrate superiority over a negative control are preferred to by the CVM. This can pose a significant barrier to the CVM's acceptance of data collected from studies conducted in foreign countries.

The second challenge is that the building blocks of dossier in other countries often different from those required in the United States. For example, requirements for submitting raw data are different in the US than they are in the EU.

Work done through VICH has helped to harmonize data requirements in key technical areas. AHI values CVM's support and active engagement in VICH. However, how regulatory authorities implement the data requirements does result in different processes that make it more difficult to submit data originally intended to be submitted to a foreign regulatory agency.

In addition, privacy laws in some other countries, like Europe's General Data Protection Regulation, don't allow sponsors to share information that US regulatory agencies often require to substantiate individual cases. These laws prohibit the collection, sharing and transfer of

certain types of data that are commonly expected to be collected and submitted in the US, for example staff CVs or an animal's medical records that may include information about the owner. This is a major problem that has the potential to limit the utility of some of the foreign-generated data by potentially removing the availability of the dossier components that are required for US registration.

AHI members recognize the challenge and difficulty that the previously mentioned points present for CVM to accept data generated abroad as substantial evidence. However, with the prior discussion on the use of real world evidence, AHI would like CVM to recognize the evaluation, including benefit risk assessment, and approval by a foreign authority adherent to the VICH guidelines. AHI proposes that CVM could consider granting a conditional approval for commercialization in the US based on the foreign data package, real world evidence and a commitment by the sponsor to present additional substantial evidence agreed upon with the agency for full approval, where applicable.

In instances where data is intended to be generated outside of the US in the future, the sponsor and the CVM could concur prospectively on the study protocol, taking into consideration the rationale for conducting the study abroad and the limitations in study design that may be required for its conduct, for example use of positive versus

negative control.

Concurrently an agreement between the sponsor and CVM could also be reached regarding the type of raw data collected in the foreign country and submitted for evaluation, taking into consideration the restrictions imposed by the local laws in foreign countries.

To conclude, AHI proposes options to better utilize foreign data as a way forward to facilitate US approval, thereby improving speed to market of potentially medically important veterinary medicines. Thank you.

(Applause)

MS. LAZO: Thank you very much. And now I'd like to invite anyone else that would like to make comments today. And we will have Rachel Cumberbatch.

Public Comment

Rachel Cumberbatch, DVM

Animal Health Institute

DR. CUMBERBATCH: Hello and thank you very much. I want to thank you for this opportunity both for this meeting and for the opportunity to provide comments on the technical aspects as well as some general comments.

My name is Rachel Cumberbatch, I am the Director of International and Regulatory Affairs at AHI. You have heard that name a few times today. And AHI is the national trade association for the manufacturers of animal health

products. This includes the contract research organizations that play an important role in conducting studies for the development of new animal medicines.

AHI commends the Center for Veterinary Medicine for hosting today's meeting, which serves as one of our first opportunities to focus discussion on key topics in alternative approaches to clinical investigations to support approval of new animal drugs.

The Fourth Animal Drug User Free Act, which we call the ADUFA, was signed into law by President Trump in August of 2018. This program benefits pet owners, farmers, ranchers, veterinarians and consumers by ensuring that FDA has the resources necessary to review and approve animal medicines in a timely fashion. These medications are vital to improving the length and quality of life for our companion animals and protecting the food supply by keeping food animals healthy.

This meeting reflects congressional interest in supporting innovative clinical investigation approaches aimed at bringing new medicines to market. It further underscores that Congress recognizes that resources alone are not enough to improve the availability of animal drugs. Process changes are needed to be modernized.

When Congress passed ADUFA in 2018, they made a key statement on the important of efficiently bringing

innovative products to market by empowering CVM to expand the conditional approval program. Under this program new animal drugs will continue to be reviewed to meet the FDA's existing gold standard for safety and good manufacturing practices. Conditional approval will enable new products that address unmet medical need to come to market as additional evidence of effectiveness is gathered.

Advancements in alternative approaches in clinical investigations will be vital to the success of this program. Submissions of these types of conditional approvals can only begin following the publication of the CVM guidance this fall. And AHI welcomes the opportunity to continue working with CVM through this expanded conditional approval program.

While ADUFA programs have been successful in many ways, we know that there is still lots of work to be done. For example, the cost to bring new animal drugs to market is rising and the number of new animal drugs approved each annum has declined. The animal health industry and regulators must work together to reverse such trends. This is an important step and AHI is ready to collaborate with CVM on efforts that will advance the work on alternative approaches to clinical investigations for new animal drugs.

Successful adoption of alternative approaches may also benefit our shared commitment to reduce the number of

animals used in research. CVM and AHI have a long history of working together on policies to advance the 3-R Principals: Replacement, Reduction and Refinement. The successful development and implementation of alternative study designs hold potential for further reducing the number of animals utilized in research and development for new animal drugs.

AHI anticipates challenges on the road to implementing innovative clinical designs but these will more than be offset by the opportunities. AHI supports drafting new guidance on adaptive study design, on the use of real world evidence and for better utilization of foreign data. We also see great value in progressing approaches that would encourage the application of biomarkers in animal health. Success in these areas can lead to increased speed to market, reduce number of animals used in testing and increase number of innovative medicines available on the market. Thank you very much.

(Applause)

MS. LAZO: Thank you, Doctor Cumberbatch. And this will conclude Session 4.

(Pause)

DR. LUCIA: Hello everybody. For those that don't know me my name is Matt Lucia and I'm the Director of the Office of New Animal Evaluation. And I just want to start off recognizing that I'm standing between us all here and being able to go home, to just take a --

(Laughter)

DR. LUCIA: To just take a couple of items. The first, of course is to say thank you very much to all of the presenters and everybody who gave such wonderful presentations and stimulated some really interesting ideas and made some very, very thoughtful points.

And I'd also like to thank all of you both in person and online, you know, thank you to those on-line who beard with us this morning when we had some hiccups and we were able to work through those. But again, thank you to all of you attending and participating in this effort. It is very much appreciated.

I'd like to also than -- echo Doctor Solomon's thanks from this morning, around the organizers of today's events. Including Susan Storey and Walt Ellenberg, who were the co-leads for this, all of the session chairs who helped facilitate the four session you heard today, as well as everyone else from CVM and here at Johns Hopkins who helped

to make today possible. It took us a year to plan this. So, there were a lot of moving parts to all of it.

I also wanted to just take a quick moment to highlight some of the observations that I had personally from the four topics that we heard today.

So, one of the -- so, first, with regarding complex adaptive and other novel investigational designs, one of the things that really resonated with me was that -- or is that the idea that there is a lot free items that we could potentially start to use today that wouldn't have implications on statistical -- or wouldn't compromise statistical integrity. And I think that there is a lot of, you know, while we continue to develop new pathways or investigate new ideas, trying to leverage more those already available and acceptable pathways is very exciting to me.

And something I heard which I thought was perhaps just a small step and just something that I am going to take back and think more about is how animal -- sorry owner consent forms are used in adoptive study designs and how those might be complicated and need to be changed several times. And what are some ways that we could through collaboration and discussion try to streamline that process more. So, just something to think about.

You know, when utilizing real world evidence I heard many times about the challenge in nomenclature

consistency. And so, one of my first thoughts was, and we also heard, you know, the word consortia quite a bit, is how can CVM or others in partnerships with our stakeholders, including AVMA, how can we advocate for nomenclature consistency which could lay the groundwork for out ability to acquire an accept real world evidence and be able to use that -- or real world data, excuse me, and be able to use that as real world evidence consistently in our animal drug approvals. And is that something that we could potentially do tangentially or along with or within, I don't know, the guidance process that we're planning to do out of all of this.

On the subject of biomarkers, I thought it was very poignant that biomarkers have to be measurable in order to be useful. And some of the challenges that go along with that is that we have to select appropriate biomarkers that are easy to collect but that are also robust enough so that they don't get compromised by all of the various or inconsistent handling and processing.

And lastly, when it comes to foreign data, how communication is key to this subject matter. And I know communication is key to a lot of subject matters, but it specifically here. And not just -- and including early communication, but not just between industry and regulators, but also between regulators amongst ourselves, continuing

those conversations so that we can identify the commonalities. And also brainstorm and discuss solutions to where our regulatory processes do not match up.

And as a very wise person said to me one time, international collaboration is the future and the future is now.

So, as Doctor Solomon mentioned this morning the -- one of the main purposes of this process is to solicit feedback and obtain information to help us put together guidances on these various issues. And I really do feel like we have heard some very, very important information that's going to help us achieve that goal.

So, this is going to be brand new information for all of you, but I'd like to remind you about the docket that you can, you know, submit comments to, that we'd really appreciate it. For those folks who have thoughts after today, you know, you're driving home tonight, or you're doing things on, for fun on the weekend and a thought pops into your mind, put it in the docket. And that's opened until August 17th.

And so with that I would again like to give a very big heartfelt thank you to everybody involved in this, both the organizers and all of you attending and wish you all safe travels home. And thank you again for making this a very successful public meeting.

(Applause)

DR. ELLENBERG: Thanks, Matt. As everybody leaves the building just please check around your seats to make sure you do not leave any items that may have fallen out of your pockets. And if you find any trash just make sure you put it away on your way out. Thank you, everybody.

(Whereupon, the meeting adjourned at 4:35 p.m.)