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DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

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CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

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VIRTUAL PUBLIC WORKSHOP – ANIMAL STUDIES FOR ORTHOPEDIC PRODUCTS

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Via Microsoft Teams Videoconference

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M E E T I N G

(8:30 a.m.)

DR. PEAT: Good morning and welcome to the Animal Studies for Orthopedic Products Public Workshop. My name is Captain Raquel Peat, Director of the Office of Health Technology 6, which is the Office of Orthopedic Devices at the FDA's Center for Devices and Radiological Health. Our office is committed to advancing innovative medical devices for treatment of orthopedic patients, in addition to addressing, for the past two and a half years, COVID-19 workload to help bring diagnostic devices, personal protective equipment, and therapeutics to patients as quickly as possible.

The purpose of this workshop is to share best practices regarding premarket animal studies for orthopedic products in CDRH, and to facilitate an open public discussion of these best practices with key stakeholders, including manufacturers, regulatory affair professionals, clinicians, members of the orthopedic community, patients, and the general public.

While this public workshop is not intended to communicate any new policies, processes, or interpretations regarding medical device marketing authorizations, our hope is that it will serve to facilitate further efforts, discussions, and collaborations towards the development and implementation of new, innovative technologies. This effort supports CDRH's vision that patients in the U.S. have access to high-quality, safe and effective medical devices of public health importance first in the world.

Today's workshop will address numerous topics intended to prompt dialogue, discussions, and collaboration. This workshop will present various considerations including anatomic specific consideration in choosing an appropriate animal model for a premarket animal performance study. Elements of complete study protocols and study reports, as describing good laboratory practice regulations, will also be discussed, as well as the role of

consensus standards and FDA guidance documents in the development and review of animal performance studies. We will also explore the importance of early and continuous collaboration with FDA in designing and executing an animal performance study best suited for meeting study objectives, it will be emphasized repeatedly in today's workshop. Our hope is that the best practices for animal performance studies to be discussed today will help facilitate high-quality animal performance data and submissions for orthopedic products.

Although this workshop will discuss best practices for animal studies for orthopedic products, we encourage sponsors to consult with us if they wish to use a non-animal testing method they believe is suitable, adequate, validated, and feasible. FDA will consider if such an alternative method could be assessed for equivalency to an animal test method.

Additionally, for studies that require the use of animals, you should consider the number of animals and the amount of data that can support the safety performance of a medical device. FDA recommends balance in the ethical principles of reduction, replacement, refinement, as well as regulatory least burdensome principles with the goal of using the minimum number of animals necessary to generate valid scientific data to demonstrate reasonable safety and performance. Thus, a thoughtful attempt of utilizing the least amount of animals that will provide meaningful interpretation is paramount. We are available to review your rationale for, and design of, an animal study as part of a pre-submission, particularly if you are uncertain regarding elements of the animal study that are important to the Agency.

I would like to acknowledge and thank the entire FDA team, including staff and leadership from CDRH's Office of Orthopedic Devices, the Office of Communication and Education, FDA studios, and other FDA contributors. I wish to also thank in advance all of today's speakers; moderators; today's Mistress of Ceremony, Dr. Kira Moore; and

Dr. Liza Fisher, Dr. Sara Thompson, Mr. Aric Kaiser, Dr. Pooja Panigrahi, Dr. Laura Rose, Dr. Laurence Coyne, and Lieutenant Commander Randoshia Miller, and everyone else in FDA who took part in planning and organizing this event, and especially to thank each one of you for participating in this workshop.

At this point in time, I would like to introduce the Mistress of Ceremony for today's workshop, Dr. Kira Moore. Dr. Moore currently serves as a health scientist on the All Hazards, Readiness and Response Cybersecurity Team in the Office of Strategic Partnerships and Technology Innovation. She originally joined FDA as a veterinary medical officer and animal study reviewer in the Division of Infection Control and Plastic Surgical Devices in the Office of Surgical and Infection Control Devices, where she specialized in assessment of animal models supporting a myriad of medical devices.

Prior to joining the FDA, Dr. Moore worked as a clinical veterinarian focused on small animal medicine, and additional training in comparative and laboratory animal medicine. She graduated with a B.S. in biology from Truman State University and received her doctorate in veterinary medicine from the University of Missouri College of Veterinary Medicine.

I will now turn the workshop over to Dr. Moore. Thank you, and I hope you enjoy the rest of the workshop.

DR. MOORE: Good morning. And thank you for the warm introduction, Captain. It is my pleasure to be a part of this workshop and I am honored to be your Mistress of Ceremony. We have an excellent program for you today and are excited to hear presentations from FDA staff, as well as special guests from the clinical community and medical device industry, on the topic of Animal Studies for Orthopedic Products.

The designated staff will monitor your comments and questions throughout this workshop. Please send your comments and questions to OHT6-Feedback@fda.hhs.gov.

Any questions or comments that are unanswered during our allotted time will be saved and addressed subsequently and incorporated into conference proceedings, as appropriate. With these housekeeping matters out of the way, we will proceed with today's program.

So it is now my great honor to introduce our first session speaker, Dr. Lisa Fortier. Lisa A. Fortier is the editor and chief of the *Journal of the American Veterinary Medical Association* and the *American Journal of Veterinary Research*, and publications division director at the American Veterinary Medical Association. She is also the James Law Professor of Surgery at Cornell University in Ithaca, New York. She is a boarded surgeon and practices at Cornell University in Ithaca, New York, and also at Cornell Ruffian Equine Specialists in Elmont, New York.

She is the recipient of the Jacques Lemans award, the New Investigator Research Award, the Pfizer Research Award for Research Excellence, the SUNY Chancellor's Award for Scholarship and Creative Activities, the Kappa Delta Award, and the American Association of Veterinary Clinicians Faculty Achievement Award. Dr. Fortier has served as the vice president of the International Veterinary Regenerative Medicine Society, and president of the International Cartilage Repair Society.

Over to you, Dr. Fortier.

DR. FORTIER: Thank you very much for having me. I have no disclosures.

There are multiple animals that can be used to test items for orthopedic research. In this 10-minute talk I will not discuss rodents, as they are not commonly used for preclinical work. What I would like to emphasize is that you have options and a lot of these options will vary, and the choice of your animal model will depend largely on your budget and on where you are located. They obviously vary by anatomy, but not that much that that will be the deciding factor. Cost will be a major factor; the age and maturity that you get the animals at, which is also directly related to cost; animal husbandry from a veterinarian's

perspective, such as boarding and handling is really crucial depending on the type of outcomes that you would like.

One of the biggest concerns is what are you trying to investigate in your product? If, for example, you have something like a manufactured osteochondral allograft that you would like to investigate, you'd like to use a larger animal model. For example, if you wanted to test a 10 mm diameter osteochondral allograft substitute for human medicine, it would be very, very difficult to use that and test that in a rabbit. The rabbit condyle is an entire -- just an entire centimeter around and so is the trochlea on its own. So for something like that, rather than rescale everything in your armamentarium, you would probably choose a horse or a sheep to replicate human. Goat, as well.

In contrast, when you're looking at something like an osteoarthritis model, a post-traumatic osteoarthritis model, and you're really looking at cartilage as an outcome measure, you can really get away with some of the smaller animal models, such as dog or rabbit, and maybe even the rat. But you can see from these schematics how the size of either the condyles and trochlea on the left or the talus of the ankle joint on the right are quite disparate from the human, which is our ultimate goal.

The first thing I like to think about when somebody asks me about choosing an animal model is physiology before anatomy, and really, I like to divide these by "are they monogastrics or ruminants?" Our experience in veterinary medicine suggests that if you have a ruminant and it's injured, they have a huge propensity to lay down a fibrin and then it turns to a fibrous response. So they're really terrific for meniscus and other soft tissue sorts of structures, but less so if you're looking at a cartilage repair model where you don't want the infiltration of fibrin and fibrous repair, or for infectious disease models because they just end up with a giant mat of scar tissue. And so for those sorts of -- the cartilage repair and the post-traumatic osteoarthritis, the models that you'd most likely tend to

would be the sheep, horse, dog, or pig.

I made similar tables like this to try and iterate what the different factors are that you might be looking at when you're choosing an animal model. If, for example, you're looking at cartilage injury such as a post-traumatic osteoarthritis model, I have, based on my experience and the literature, ranked these animal models as 1 as best and then increasing numbers as they are less ideal for the specific item that's being scored.

So for example, cartilage thickness. The pig and the horse are closest to the human. I know that the literature says sheep and goat are close to humans. I've operated on hundreds and hundreds of sheep and goat and I find them really highly variable. So again, if you are looking to analyze cartilage, sometimes sheep and goat cartilage can be super thin and other times it does approximate 1 to 2 mm. The rabbit would be super, super thin and dog would be in between.

And then you can keep going down the different columns and see what things are being analyzed here. So tissue quantity, if you just want to look at cartilage and just histology or maybe some imaging, then you want -- then you could look at the rabbit and that would probably be plenty. But if, for example, you wanted to look at -- or sorry, for tissue quantity overall, let's say you want to look at subchrondal bone, synovial fluid, synovial membrane, you'll need a larger animal model such as a horse or a dog. Rabbit would be the least ideal and then of course, rodents, which are not a focus of this talk.

Cost is highly, highly variable depending on the area that you are living at and where your animal model study is going to be performed. The other thing to consider in cost is do you want these animals to be mature at the time of sourcing them and if that's true, then pigs rank very, very high, meaning they have a high score, so they're not ideal if you want them to be mature because they can be quite expensive to source as a mature animal. So cost overall, for sure, the rabbit would be the lowest followed by sheep and goats because

you can house them, several of them in the same pen, followed by the horse and the dog.

If you want to do longitudinal in vivo, some type of analysis such as imaging, synovial fluid, gait analysis, such as shown on the right with the pig walking on the treadmill, I've tried to get sheep and goats over treadmills, that's a real hassle, not very usable data. Horses and dogs would be the best for longitudinal outcome.

And then maybe you want to have a look at the cartilage, as well. So again, ranking them of 1 was optimal, followed by 2 and then so forth, and then they're totaled up. And so for cartilage injury, for post-traumatic osteoarthritis, the pig and cow rank as the best, followed closely by the dog, then the sheep and goat and rabbit. I'm not saying that sheep and goat aren't good. Just when you look at all of these things combined, the pig and horse are probably a bit better.

Now, when you're looking at cartilage or osteochondral defects, so cartilage repair versus -- in the previous slide, I was discussing post-traumatic osteoarthritis, so the only thing that's different in this table is the addition of bone because if it's cartilage or osteochondral, even if you have a cartilage injury, you're going to be trying to look at the bone and the bone repair, as well.

And so when you look at that, sheep and goat are probably the closest. Horses have pretty stiff bone, people know that. It's doable, but you need special instrumentation, but it is definitely doable. So sheep, goat, and dog are probably the best ones. Again pig, not great, because you have to source them as adults, otherwise you have very soft bone. And rabbits are pretty well known for bone to heal quite rapidly. So now the re-ranking ends up to be that the horse, pig, and dog rank up there, sheep is very close behind, and the rabbit.

You can see this growth chart that I have taken from a bio-source where we get our pigs from and they're really, really rapid growth. So if you're trying to do a bone, anything to do with bone, they'll heal, their bone will outgrow anything that you put in there, so not

ideal at all for an osteochondral defect.

Also quite difficult when you're trying to do different types of dosing, even for non-steroidals or sedation or any of those things, you really have to weigh them every day, every couple of days, or at least the day before you're going to do any intervention; otherwise, you're constantly under-dosing them because they grow so rapidly.

Bone defect fracture repair, anterior cruciate ligament repair, or shoulder soft tissue injury, I'm not going to go through all of those tables again, but rather highlight some of the unique things to each of these animal models.

By far, the most commonly used animal for bone repair and fracture would be -- in a large animal, would be the sheep. We all know that they have fibrolamellar bone throughout their life. It's just something you have to control for and know about when you start to look at it on histology. There are many studies documenting this in every different bone in the sheep. Dogs are a decent model as well, followed by rabbits.

Again, going back to the pigs, this is recent data within the last couple weeks where I looked up what it costs for an adult. Yucatan mini-pig, in this area in New York, as an adult at 24 months of age would be about three and a half thousand. If you want a Göttingen mini-pig, it's up to eight and a half thousand dollars for one mature pig. On top of that, pigs are a real nuisance to each other. Anything you try to put on, such as a bandage, an external fixator, anything like that, they have to be housed separately otherwise they'll knock it off of their next door neighbor, even IV catheters. So their husbandry can be quite difficult, as well.

Goats are not my favorite, by far, because they're really, really curious and intelligent, they're constantly jumping, they'll jump on each other, they'll climb walls if you try to environmentally deprive them. These are patients of mine in the hospital, like orthopedic patients at Cornell, and they are just really difficult to try and manage. There

are some goat herds that would be more calm, but if I had to choose between the sheep and the goat, I'd pick the sheep. Horses are an abysmal model for anything to do with bone repair. They have to be weight bearing on all four limbs. You can use them for small non-weight bearing segmental defects, but not for something really like fracture repair or testing anything like a bone defect model.

For tendinopathy, again, you want the animals that have a large enough tendon such as a superficial profundus or an Achilles that you can get to and you can manage. So horses are really a great model for tendinopathy because you can do so much and then for husbandry wise, you can do so much without sedation or with very light sedation. Sheep are not a bad model. They have that fibrous response, so you will get a vigorous repair tissue, but they're not a bad model at all for any type of tendinopathy. Dogs are pretty good, and so is the rabbit for Achilles.

Again, going back to the goats, they're just a bit naughty, showing you again more goats that are climbing. And I would say the same for the pigs. On top of that, pigs, they are rapid growth if you're going to use them for an Achilles model, and then back to the nibbling on the bandage method all the time. But pigs are very, very easy to train, they're obviously super-smart animals and you can train them to go over a pressure mat or a force plate really readily, so you can get a lot of good outcome data from pigs.

In meniscus, immobilization is really, really critical so again, it goes back to animal husbandry. We can put sheep and goats, if we want to, in the Velpeau or the Ehmer slings that are shown here. Sheep also are quite immobilized and that dark sheep in the middle with the blue bandage on, on the right hind limb, if you just put a heavy Robert Jones on and really lock that hind leg, straighten out the hock and the patellofemoral joint, they'll walk around quite nicely in an unloaded position and they'll tolerate that really well. The sheep in the upper left-hand, half of my sheep have tolerated a bandage such as this and

others kick at it constantly, which creates more stress for the sheep and probably worse for your repair than just having them in a Robert Jones. So I've really gone to more of like the sheep, the dark sheep with the blue bandage. Goats again climbing on everything. Rabbits can be very difficult to immobilize for a meniscus repair. I've done some meniscus studies, especially for DMM, but for post-traumatic osteoarthritis, but not necessarily meniscus repair in a pig because the pigs that I can source are very rapidly growing. And then again, horses would not be a great model because you cannot immobilize their hind limb and it's just not necessary to use that large of an animal model for a meniscus repair.

What I would like to say is, in the end, you have options. I would like to suggest that you consult at least a veterinarian, if not an orthopedic surgeon, if you're going to do something. Like in a large animal study consult large animal. Most of us, as veterinary orthopedic surgeons, know the fundamentals of all the different animal models but certainly, before you go into a pig or a sheep or a goat model, it would be best to consult with a large animal person. And I thank you for your time.

DR. MOORE: Thank you, Dr. Fortier, for that very interesting anatomy presentation.

We will now hear the perspectives of industry on considerations for animal study designs. Dr. James Cook, Director of the Mizzou BioJoint Center, Director of the Thompson Laboratory for Regenerative Orthopaedics, and the William and Kathryn E. Allen Distinguished Chair in Orthopaedic Surgery. He received his bachelor's degree from Florida State University, completed his D.V.M. in 1994 and his Ph.D. in 1998. In 1999, he founded the Comparative Orthopaedic Laboratory at the University of Missouri, a multidisciplinary team of physicians, veterinarians, engineers, and basic scientists dedicated to translational orthopedic research. He is also co-founder of the Be The Change volunteers, an NGO dedicated to building schools in remote villages in the developing world. His teams have built 56 educational facilities in 17 countries, providing educational opportunities to more

than 7,000 students.

Dr. Cook, the floor is yours.

DR. COOK: I'm very honored to be part of this FDA workshop on animal models for orthopedics. I'm Jimmy Cook from the University of Missouri and I'm going to cover the topic of considerations for animal model study design.

My related disclosures are listed on this slide. I have not received commercial support related to this talk.

The first question that we have to address is why we need to use animal models for investigating orthopedic problems and their potential solutions. Many people wonder, with all of the technology and advances made using cell and tissue cultures, robotic biomechanical testing, and computer modeling, why can't we just go from those to human use. The answer is that while these types of studies are very useful for providing critically important preliminary data for screening, prioritizing and optimizing mechanisms, drugs, devices, and biologics for potential clinical application, they are not sufficient for determining safety and efficacy for use in patients. And that's why regulatory bodies like the FDA require well-designed, ethical animal model studies that provide valid preclinical data prior to any clinical implementation of these methods and products.

Animal models provide clinically applicable data that enhance the likelihood for safe and effective outcomes in clinical trials. And to me, another great benefit of performing robust preclinical animal model studies is that the results can then be safely and effectively applied to veterinary patients in order to help the many animals affected by the very same orthopedic disorders, too.

The next question then is which animal model should we use. Well, that's going to depend on a number of variables, starting with the goals and hypothesis of the study, which then determine the experimental design. The capabilities and familiarity of the institution

and investigators regarding different animal models are also very important with respect to ethical and effective animal studies. These core components significantly affect the translatability of the results, which is also highly influenced by other key variables including whether the model is based on spontaneously occurring pathology or surgically induced lesions, skeletal maturity and age of the animal, the relevant anatomy and biomechanics, and other often overlooked factors such as postoperative pain management, restrictions and physical therapy, the GI physiology of the species chosen as it may relate to pharmacokinetics and pharmacodynamics, types and assessments of complications and side effects, and standardization validity and clinical relevance for key outcome measures. And it is critical to consider what the feasible and ethical controls and comparisons will be. This is such a key component of study design that unfortunately, is not always carefully considered.

In general, a placebo or a sham procedure should be used for study design to evaluate safety so that the experimental group can be assessed against something that does no harm. For efficacy studies, a standard of care comparison should be used whenever possible and ideally, pivotal studies include both these positive and negative controls. For example, a study design to assess safety and efficacy of platelet-rich plasma for treatment of knee osteoarthritis would include saline and hyaluronic acid controls. And a study design to assess safety and efficacy of a novel scaffold for rotator cuff repair would include debridement and direct repair controls.

Of course, this is not always appropriate, such as for an animal model study evaluating immediate surgery versus surgical after medical optimization in canine patients suffering spinal fractures for which a sham surgery negative control would not be ethical. In addition, sometimes the reference standard is a very poor comparison, such as microfracture as a control for cartilage repair and restoration techniques, or does not

model the intended target well, such as the use of untreated ACL transsection needs for study of primary osteoarthritis. The number, type, and reproducibility of study controls strongly affect the required sample size for a robust, valid, and applicable study design.

At this point we carefully reassess our capabilities and familiarity with all components of the potential models and work closely with the Animal Care and Use Committee to determine best practices. The investigators' and facilities' capabilities regarding animal husbandry and enrichment components are critical, not only for ethical animal research, but for validity and applicability of the study results. I strongly recommend to involve a knowledgeable veterinarian and end-user physician in these assessments.

After analyzing and assessing these key factors, we work toward a comprehensive stepwise approach to animal model study design. We start with a clinically relevant research question that generates study goals, specific aims, and corresponding hypotheses. Then we categorize the study with respect to primary purpose or application which may involve one or more of those listed in the column on the left. Based on these initial steps together with access, availability, and capabilities, all of the other components of experimental design can be readily determined and applied. This is the point where discussions with the sponsor and/or respective regulatory agencies should be frequent and thorough to ensure expectations and requirements are clear and will be followed.

If your laboratory has a specific focus for animal model studies, algorithms, like the ones shown here, can be created based on the stepwise approach discussed in order to make experimental design and communication efficient.

When designing a preclinical animal model study, I do think it's important to determine what the perfect model would be. To me, these are the key components for an ideal animal model study designed to comprehensively evaluate safety and efficacy for

clinical application. Of course, it's very rarely possible to accomplish this goal, so it's important to prioritize and then include the key components that you are able to, while being very transparent about the limitations associated with those that you are not able to. Many of the limitations are out of our control, so it's just important to realize what those are and account for them in experimental design analyses, reporting, and application of the study results.

With all of this in mind, the 3Rs for ethical research involving animals must then be applied. For us, this means starting with in vitro, ex vivo, and in silico models whenever possible, moving to screening studies that prioritize safety and feasibility assessments, then on to preliminary studies that validate safety, support efficacy for intended indications, and provide data for determining appropriate sample size for pivotal studies designed to address scientific, regulatory, and market-based components for implementation in clinical trials.

If this process results in progression to a pivotal study, the key considerations include the use of skeletally mature large animals with a defect or lesion that has been validated such that it is symptomatic and will not spontaneously resolve. Pivotal studies need to have robust and relevant controls and/or cohort groups, be of at least 6 months duration and include diagnostic imaging, clinical, functional, gross, biomechanical, and histologic outcome measures and be performed using GLP-level documentation.

We also have some non-negotiable requirements for our use of canine models. Of course, the care and use of these animals has to be ethical and respectful in all ways by all involved. We always implement a number of enrichment activities including walking with a handler and group interaction time. And then we make sure that all of these studies have maximal impact by including the use of tissues that would otherwise be discarded for in vitro and ex vivo studies, and applying study results to veterinary patients so that the

research helps animals, too.

So let's go over some examples. A very prevalent problem in humans and dogs is low back pain from intervertebral disc degeneration, and the anatomic, pathologic, and diagnostic similarities become readily apparent when I rotate and magnify the canine MRI. There are a myriad of questions surrounding this problem, but the clinical research question we wanted to attack first was whether or not we could develop mechanistic biomarkers to serve as effective screening, early diagnosis and/or staging tools so that more effective prevention and treatment strategies could be validated and implemented.

Unfortunately, several different breeds of dogs are very commonly affected by intervertebral disc degeneration with two distinct phenotypes noted clinically. Chondodystrophic breeds such as dachshunds and beagles, and non-chondodystrophic breeds such as German shepherds and Labrador retrievers, have similarly high rates of symptomatic intervertebral disc degeneration but differ in presentation, timing, and pathomechanism. Fortunately, each of these phenotypes corresponds well with those seen in human patients and therefore provide excellent models for research that can help both species.

So we first wanted to see if it was feasible to develop mechanistic biomarker panels that could distinguish disc disease from normal and further define clinical relevant phenotypes in human and canine patients. So hopefully, it is easy to see how these initial steps help determine the nature of the model, characteristics of the research subjects, and the outcome measures with a single time point cross-sectional study.

For this study, we look at protein biomarkers in serum, urine, and cultured disc tissues from diseased canine and human patients, and normal tissue donors. So if we just look at two representative samples of the 40-plus biomarkers that we analyzed, you can get a feel for the biomarker profiles we were able to create and compare for healthy and

diseased human and canine intervertebral disc phenotypes. The results of this study allowed us to conclude that dogs can serve as robust translational models for clinically relevant intervertebral disc disease research in both species, that CD dogs model phenotypes of IVD degeneration in young human patients and NCD dogs model phenotypes of IVD degeneration in older human patients. The biomarkers can explain pathomechanisms for pain and structural degeneration and they are shared between species, and this animal model and approach provide a feasible pathway for pursuing targeted research towards early diagnosis, prevention, and treatment for both species.

The next example targeted the clinical research question surrounding the high failure rate for current methods of treatment for large retracted rotator cuff tendon repair. Despite extensive research and numerous technological advances in this area, failure rates for these large retracted, often referred to as massive, tears as high as 70 to 90% have been reported after directed care using many different techniques.

In our eyes, one of the limiting factors to addressing this major unmet need in orthopedic health care was the lack of a robust large animal model for this common orthopedic problem. So we developed a model that could achieve this combination of goals which required a surgically induced infraspinatus tendon release that was tagged and allowed to retract, resulting in tendon and muscle atrophy with fatty infiltration in purpose-bred research hound assessed using comprehensive, clinically relevant outcome measures and time points.

Once this chronic, massive, retracted rotator cuff tear was validated to result in a critical lesion, we were able to use it to test a number of different preclinical and postmarket treatment strategies such as this biologic scaffold combination using comprehensive outcome measures. Taken together, these studies allowed us to conclude that this preclinical canine model is valid for the study of large, retracted, chronic rotator

cuff tears as it mimics key features of this disorder and allows for use of current clinical repair techniques. Using this model, we have been able to show that bone-tendon allografts and biologic scaffold repairs are effective for achieving consistently successful functional outcomes by improving the tendon-to-bone healing.

For the final example, we will target our translational research aimed at addressing the clinical research question of why meniscal allograft transplants fail in about 20% of cases. We know that the typical modes of failure for the frozen meniscus allografts used currently involve graft shrinkage, extrusion and/or tearing. But it is unclear what biologic and biomechanical mechanisms underpin these clinical failures.

So we set out to develop a preclinical model for meniscus transplantation that could elucidate mechanisms for failure and allow for the assessment of safety and efficacy of novel grafts and techniques in purpose-bred research hound using comprehensive, clinically relevant outcome measures and time points.

With Department of Defense funding, we used our previously validated arthroscopic meniscus release model to surgically induce meniscus extrusion and medial compartment cartilage pathology and then compared three different meniscus allograft transplantation techniques. Arthroscopic, MRI, gross, and histologic outcome measures provided evidence in support of the validity of this preclinical model for study of meniscus allograft transplantation. The use of fresh, viable meniscus allografts can be safe and effective, and mechanisms for superior outcomes with respect to knee joint health and function, and mitigating failure involved biologic and biomechanical factors including live cells, intact extracellular matrix, and reconstruction or maintenance of the meniscal tibial ligament; these evidence-based advances have been translated into successful clinical use.

In true trial principles for use of animals in research, we have directly applied the results of these studies to benefit all of these and many other veterinary patients, as well.

Of course, none of this work would ever get done or be used to help human and veterinary patients without the amazing team that I am blessed to work with at the University of Missouri, so my greatest thanks go to them. And again, I'm extremely grateful to the organizers of this FDA workshop for allowing me to present.

DR. MOORE: Thank you for sharing those insightful perspectives, Dr. Cook.

Our next presentation will be an overview of orthopedic specific models for extremities. It is my pleasure to introduce Dr. Natalie Miller. She is a veterinary medical officer here at FDA where she works as an animal studies reviewer primarily for medical devices in the cardiovascular space. She graduated from the University of Pennsylvania V.M.D./Ph.D. program in 2013 with a Ph.D. in cell and molecular biology from the MVP group. Prior to joining FDA in 2015, she worked as a clinical veterinarian and a livestock export manager, building both her clinical and regulatory skills.

Since 2015, her focus at FDA has been the review and regulation of structural heart devices such as heart valves and cardiac occluders. In addition to her review work, she has helped to establish a center-wide community of practice for animal studies review designed to help train new reviewers, maintain review consistency, and facilitate study design in animal model related conversations. She also works as a medical device reporting (MDR) analyst reviewing reported adverse events to help maintain patient safety over the entire lifespan of medical devices.

Just a quick reminder, please use the OHT6-Feedback@fda.hhs.gov e-mail to send in your comments and questions.

And now, Dr. Natalie Miller.

DR. MILLER: Good morning, my name is Natalie Miller and I'm a veterinary medical officer for OHT 2, the Office of Cardiovascular Devices within the CDRH. Today I'll provide a high-level overview of a few of the animal models commonly used in the evaluation of

orthopedic products. Next slide.

Please note that this presentation is an overview and does not reflect specific requirements for preclinical animal studies that are submitted as part of an application to support premarket clearance of an orthopedic product. In addition, we encourage applicants to consult with us if they wish to use a non-animal testing method that they believe is suitable, adequate, validated, and feasible. We will consider if such an alternative method could be assessed for equivalency to an animal test method.

When considering the number of animals and the amount of data that can support the safety and performance of a medical device, FDA recommends balancing the ethical principles of reduction, replacement, and refinement, as well as regulatory least-burdensome principles with the goal of using the minimum number of animals necessary to generate valid scientific data to demonstrate reasonable safety and performance. For more information about bone void fillers and cartilage repair products, please see our bone void filler special control guidance and cartilage repair guidance documents. Next slide.

The objective of my presentation today is to provide a high-level overview of two defect models in extremities, including best practices for implementing these models. First, I will talk about considerations that apply to both defect models. Then I will provide an overview on study design considerations for femoral defect models which are commonly used for the evaluation of bone graft substitutes, and considerations for cartilage defect models which are used for the evaluation of cartilage repair products. I've included tabs at the bottom of my slides to show what applies to both bone and cartilage studies, what applies solely to bone studies, and what applies solely to cartilage studies. Next slide.

The critical-sized bone defect model is commonly used to evaluate bone grafts and bone graft substitutes. Bone grafts and bone graft substitutes are used for a variety of indications in orthopedic surgery, particularly in oncologic surgery, traumatology, revision

prosthetic surgery, and spine surgery. Bone is the second most frequently transplanted tissue behind blood, and more than 500,000 bone-grafting procedures are performed every year in the U.S. The number of available products and the amount of published information about bone graft substitutes can complicate surgical decisions regarding bone graft substitutes.

Although autologous cancellous bone represents the gold standard for bone grafts, there are significant disadvantages associated with their use, including limited amount of graft material, prolonged surgery time, and donor site morbidity. Allografts are available; however, these may cause immunogenic reactions and may transmit infectious diseases. To overcome these limitations, bone graft substitutes have been developed. The ideal bone graft substitute strikes the perfect balance between bone formation and biodegradation. Because none of the available synthetic bone graft materials perfectly encompass every desirable attribute for the ideal bone graft material, there's increasing interest in the research and development of new biomaterials. Next slide.

An estimated 9% of the United States population age 30 and older have clinical osteoarthritis and it is the leading cause of disability in the United States. Osteoarthritis leads to pain, loss of function, and decreased quality of life. Additionally, osteoarthritis costs an estimated $303 billion annually in medical costs and lost earnings.

Osteoarthritis impacts articular cartilage, which gets severely degraded over the course of the disease. Articular cartilage is the smooth cartilage at the ends of the long bones. Because this cartilage has a limited healing capacity, damage or wear to the native cartilage creates defects that heal very slowly, if at all.

Because there is no cure for osteoarthritis, treatment is directed at managing its progression and mitigating the pain and impaired mobility that it causes. The development and evaluation of novel cartilage repair devices using established animal models is critical as

we search for ways to manage this debilitating disease. Next slide.

The next slides will cover animal model considerations that apply to both bone and cartilage defect models. Next slide.

The animal studies utilized for assessment of orthopedic devices typically provide initial evidence of device or product safety, their potential performance when used in a living system, and the biologic response that a living system may mount toward the device. For some devices such as bone void fillers, animal data can be adequate to support performance for a regulatory submission and serve as the sole source of in vivo performance data. For others, such as the cartilage repair devices and products, animal studies are generally conducted to support initiation of a clinical study and to complement the data collected in that study. Next slide.

Regardless of the role of the study, there are key considerations that would apply to these critical bone defect and cartilage defect studies. Humane animal care and use, as well as the practice of refinement, reduction, and replacement, should be central to every animal study. A well-designed and well-controlled study using an appropriate animal model is a key component to the reduction of animals that are sacrificed during the development and safety evaluation of medical devices. Next slide.

Use of a reproducible and validated animal model ensures that the data obtained from the study will help us draw conclusions about the performance of the device or product. Although there is no FDA-recognized standard for the cylindrical drill defect model in bone, there is an FDA-recognized standard for in vivo assessment of implantable devices intended to repair or regenerate articular cartilage: ASTM F2451-05. That standard provides information on animal models and outcome measures, but does not provide detailed information on study design considerations for cartilage defect animal models. Unlike posterior lateral spine fusion standard ASTM F3027, there are no standards that

provide a similar level of detail about the study model and protocol. Validated animal models for evaluating orthopedic devices are well characterized in the literature, though. However, a PubMed search can be overwhelming, churning out thousands of references, each of which represents a wide array of animal models, methodologies, and evaluation endpoints. Next slide.

Regardless of the animal model chosen, the defect should represent a critical-sized defect, which is a defect that will not spontaneously heal. Using a model that won't heal spontaneously allows us to have a baseline for the healing response so that we can judge the impact of the device or product.

For bone, Hollinger et al. defines a critical-sized defect as one which has less than 10% bony regeneration during the lifetime of the animal. Cartilage defects have more inherent variability in both diameter and depth, and there's less consistency in the cartilage dimensions in the literature. This variability may be due to the broad range of cartilage repair devices with different methods of deployment. For example, some cartilage devices are anchored into the underlying subchondral bone, and the corresponding empty defect would need to be deeper than a device that is intended for use more superficially.

The dimensions of critical defects differ between species and anatomical locations. The larger the species chosen, the larger the defect must be in order to represent a critical defect. The size of the defect chosen should be based on documented evidence either in the literature or from use of prospective concurrent negative control defects, also known as MT defects. Next slide.

Because of biologic variability and the difficulty in executing these studies, including an MT defect negative control group, confirms that the critical defect model has been properly implemented, as well as provides baseline numbers for comparison. We recognize the need to limit animal numbers; however, the use of concurrent negative and positive

controls is strongly recommended for any pivotal preclinical animal studies. This is because it is generally not possible to account for all confounding factors that are introduced with a non-concurrent control arm, and the results and bias prevents us from drawing meaningful conclusions about device performance.

In addition to the MT defect negative control, a positive control comparator group should be included in the study design. The comparator may represent the current standard of care or a device that's similar with respect to technological characteristics such as composition or configuration. Using devices or products with similar technological characteristics helps ensure that you capture similar time course events in terms of healing response, new tissue formation, and device resorption, to allow for a more accurate comparison. Examples of appropriate positive control devices include, for bone void fillers cleared under 510(k), this could be a predicate with similar technological characteristics or autograft. For cartilage repair devices, this could be an approved cartilage repair device or standard of care. Next slide.

The age of the animal studied is an important consideration to ensure the results support the intended clinical population. During an animal's growth, bone undergoes dynamic changes in metabolism and remodeling which can impact the tissue repair and introduce biases that can impact our evaluation of device or product performance.

When you're evaluating the performance of an orthopedic device intended for use in an adult population, the animals chosen for investigation should be skeletally mature. Because weight charts can give a premature indication of skeletal maturity and animal weight can vary between suppliers, radiography to document closure of the tibial growth rates should be performed to confirm skeletal maturity prior to implantation. If radiographs are not performed prior to implantation, the animal should be sufficiently old to ensure skeletal maturity. For rabbits, which are commonly used in bone defect models,

they should be greater than 9 months of age. For ruminants, which are commonly used in cartilage defect models, they should be greater than 3 years of age. For canines, which are also used in cartilage studies, skeletal maturity should be obtained by 18 months of age. Next slide.

Pilot studies and bench testing are valuable tools to inform the study design choices for a pivotal animal study, particularly with regards to animal numbers and experimental groupings. It is important to include adequate animal numbers to obtain predictive outcomes while being mindful of the 3Rs: refinement, reduction, and replacement. Our goal is to use the smallest number of animals that will provide meaningful interpretation of the data.

If the device material is well characterized with a history of safe use and you anticipate minimal variability in the device performance, you may be able to use fewer animals. However, if you anticipate a large degree of variability or if the device material is new and not well characterized, additional animals may be required.

The types of testing may impact the animal number, as well. Biomechanical testing is recommended when evaluating cartilage repair devices but those tests are often destructive, impacting the histological evaluations of the implant site. Thus, separate study groupings may be needed to allot a separate subset of animals for destructive mechanical testing. Although this may increase the number of animals in the study, it's an important aspect of establishing the safety profile of a cartilage repair device. Next slide.

Evaluation time points should be chosen with consideration for the device material composition, the length of implantation, and the rate of degradation when applicable. In most animal studies, a minimum of three evaluation time points is recommended. The earliest time point will allow for an assessment of the initial biologic responses to the device. An intermediate time point should establish interim device behavior between

earlier and later time points, as well as document a reduction of any initial inflammatory response. For resorbable bone graft substitutes, the final time point should be of a sufficient duration to demonstrate bone and tissue healing and to characterize the effects of any residual device material. It is understood that the final time point may not allow for complete device resorption; however, the compilation of all the time points should demonstrate a trend toward complete device resorption.

For most bone void fillers, three time points at 4 weeks, 8 weeks, and 12 weeks are adequate to evaluate the device performance but can be shifted to better capture the expected resorption profile of the material. For fast-absorbing material such as calcium sulfate, shorter time points of 2, 4, and 8 weeks may capture resorption, while longer-absorbing materials like hydroxyapatite may need longer time points of 8, 12, and 26 weeks. Additional time points may be needed to allow for a more complete assessment of the biologic response and characterization of device components at relevant times, particularly if the device contains a novel material.

For cartilage repair products, studies that are a minimum of 1 year in length are recommended to provide an adequate period for completion of healing but still have at least three time points. This duration is also generally sufficient to allow assessment of durability of the therapeutic response and of the integrity of the product during extended weight-bearing and cyclic loading. As we discussed before, cartilage animal studies are typically the precursor to clinical data and used to support initiation of a clinical study. So this extended study duration provides confidence that the device or product is ready to be tested in humans. Next slide.

All orthopedic animal studies, regardless of device type, require daily in-life observations such as overall appearance, body weight, appetite, and pain assessments. Additional study endpoints are determined by factors such as the device type and the study

objectives. Often, clinical pathology and organ pathology data are also collected to evaluate the device biocompatibility, thereby minimizing the number of animals that must be sacrificed. Clinical data is rarely indicated prior to clearance of a bone void filler for use in humans. Therefore the animal data endpoints must provide a clear picture of the projected safety and clinical performance. A femoral defect study should include imaging such as radiographs, plus or minus micro-CT, gross pathology, histology, and histomorphometry. Because bone void fillers are for defects that are not intrinsic to the stability of the bone, mechanical data is usually not needed.

Cartilage repair products often require clinical data to support device safety and performance. Therefore the study endpoints should mirror those chosen for the clinical study. Examples of endpoints that are often included in evaluations of cartilage repair products are kinematic analysis, imaging such as radiography or MRI, arthroscopy, synovial fluid evaluation, histology, gross pathology, and biomechanical testing. As with bone defect studies, clinical pathology and organ pathology data may be collected during cartilage defect studies to evaluate the product's biocompatibility. Next slide.

The next slides will cover animal model considerations that apply specifically to the bone defect models. Next slide.

Each animal model has its own unique advantages and disadvantages. The ultimate goal of the chosen animal model is to produce results that can be translated to clinical practice. For example, one must consider whether the bone metabolism and structure of the animal chosen is sufficiently similar to allow a meaningful comparison and extrapolation of data to the clinical use. Rats and mice are inexpensive and easy to handle; however, rodents are often too small to test degradable materials in bone. Furthermore, rats and mice experience continuous bone growth throughout their lifetime. Thus, they are not well suited to evaluating products intended to form bone over time. Rabbits are very commonly

used to evaluate bone graft substitutes for use in both extremities, as well as the spine. Although care of the rabbit is more expensive than that of rodents, they're more economical than larger animal models. Rabbits are one of the smallest animals that have similar bone morphology and anatomy to humans. The anatomy and physiology of canine long bones readily translates to that of humans; however, canines are companion animals, giving rise to ethical considerations that limit their use in preclinical animal studies.

The cost of animal care increases with the size of the animal, but the larger animals often share more similarities in size and biomechanical forces with the human bones. Small ruminants such as sheep and goats have a similar body weight and bony macrostructure to that of humans, but the microstructure of ovine bones is slightly different. One advantage to small ruminants is that their repair rate is more comparable to humans than that of the smaller species. Other animals that have been described in the literature include pigs, horses, and non-human primates. Next slide.

The location within the bone chosen for implantation is another important consideration that should be considered based on the intended use of the product or device being evaluated. If the bone graft substitute is a bone void filler which is intended to fill bony defects that are not intrinsic to the stability of the bone, an epiphyseal defect is more appropriate. There is both cortical and cancellous bone present in the epiphysis, where the diaphysis is primarily cortical bone. Evaluating the device in an anatomical location that includes both types of bone allows for a more complete profile of the device safety and performance. While the femoral condyle is the most common site for implantation, the use of many different types of bones has been described in literature, including the humerus, tibia, and ulna. Next slide.

Today's discussion focuses on the protocol for cylindrical defects in the femoral condyle, which is one of the more commonly performed defect models to evaluate bone

void fillers for use in extremities. This protocol can easily be modified for implantation in bones and alternative anatomical locations. The animals must be anesthetized and the limb is prepped for surgery. Blunt dissection is performed to expose the distal femoral condyle. Either the medial or the lateral aspects of the femur are appropriate for this model. A cylindrical drill-hole defect is created, starting at the cortical shell and extending into the underlying cancellous bone. Sterile saline irrigation should be applied concurrently to act as a coolant and to protect the surrounding tissue from thermal damage.

Following creation of the defect, the graft material is packed into the defect site, filling the defect to the height of the cortex. The device is prepared according to the labeling with separate test groups if the device is mixed with bone marrow aspirate or autograft. Finally, the overlying soft tissue and skin is suture closed. A post-implantation radiograph is important to confirm the appropriate placement of the graft material within the defect, as well as establishing the baseline appearance of the bone-graft interface. Next slide.

The presence of periosteum can influence the bone and tissue healing within the defect. Thus, it is important to consider whether the periosteum will be preserved during the creation of the defect. The periosteum is highly vascularized and provides the cortical blood supply. Studies show that removal of the periosteum leads to a 73% decrease in new bone and cartilage, a tenfold decrease in new vessels, and a 75% decrease in osteoblast. Because the periosteum can have significant impact on the performance of a bone graft material, it is typically removed during the studies of segmental defects. The handling of the periosteum should be consistent throughout the study, regardless of whether the periosteum is preserved or removed. Next slide.

When performing a pivotal study to support the device's proposed indications for use, the animal study should deploy the final finished sterilized form of the device under

investigation. Many bone graft substitutes are labeled to be combined with autograft and/or bone marrow aspirate. Many products also require hydration or reconstitution prior to deployment, such as with bone marrow aspirate or mixing with autograft. If mixed with anything other than blood or saline, the device should be evaluated under each labeled condition following the recommended ratio of each component as reflected in the labeling. Next slide.

At a minimum, a bone void filler should be evaluated using imaging, histology, and histomorphometry. Radiographs are used to provide an overall high-level, nondestructive assessment of bone formation, graft resorption, device-graft location, and device-graft migration. Although plain X-ray may be sufficient, the addition of micro-computed tomography, or micro-CT, can provide additional three-dimensional detail and quantitative information on device microarchitecture and tissue in-growth.

Histologic analysis can provide a qualitative analysis of the types of tissues present and confirm the presence of bone rather than calcified tissue and residual implant throughout the defect over time. Prior to processing the samples for histology, gross examination of each specimen should be performed. Histologic samples should be taken from multiple locations throughout the defect, either by a single longitudinal section through the saggital plane or multiple transverse sections incorporating the middle of the device, of the defect, and each of the outer boundaries.

Although both longitudinal and multiple transverse sections can capture the stained areas of the defect, a single longitudinal splice requires near-perfect technical execution to ensure that it enables comparison between animals. However, obtaining well-executed single longitudinal sections is extremely technically challenging, so we recommend multiple transverse sections.

Multiple stains such as H&E and Masson's trichrome may be used to ensure each

tissue type is captured and identified. H&E is better for general tissue evaluations, while a bone-specific stain is used for histomorphometry to provide a quantitative assessment of bone formation and graft material.

As with the qualitative histology, histomorphometric analysis should be representative of multiple slices obtained at different levels throughout the sample. For each histological evaluation, the region of interest should be clearly defined, consistent, and exclude any areas of host bone. Each study animal should be included in every evaluation endpoint. This concludes the bone defect specific section. Next slide.

The next slides will cover animal model considerations that apply specifically to cartilage defect models. Next slide.

Choosing an animal model for the evaluation of cartilage repair devices is challenging, as there is no perfect animal model for articular cartilage injury. Cartilage defect models have been described in many different species including rats, rabbits, canines, sheep, goats, pigs, and horses. Larger animals are more appropriate for a pivotal study because large animals have articular surfaces and thickness sufficiently large to adequately investigate and optimize the formulation, design, dimensions, and associated instrumentation envisaged for human use.

While the horse most closely approximates the cartilage thickness of the human, ethical considerations and cost of care generally limit their utility in preclinical research. Similarly, the canine model, while useful, is often avoided because of the dog's role as a companion animal. The most commonly used animal models for evaluation of cartilage repair devices are sheep and goats. While sheep are more docile and easier to handle, the thicker articular cartilage of the goat is more representative of the human cartilage thickness. In addition, small ruminants such as sheep and goats are similar in size and weight to a human subject. Although they are quadrupeds, the mechanical load of the

small ruminant is more representative of the human mechanical load than that of a rabbit or rodent. This is particularly important as mechanical load has been shown to impact cartilage development and maintenance, as well as cartilage degeneration. Next slide.

Although contingent on your Animal Care and Use Committee, the use of a bilateral defect model is becoming increasingly acceptable with appropriate analgesia and postoperative care protocols. While a bilateral model may reduce total animal numbers, unilateral models may be less stressful for the animals and allow for evaluation of lameness and gait analysis during the study. Each of these factors should be carefully considered when designing a pivotal study. Next slide.

The animals are anesthetized and the area is prepped for surgery. There are several approaches to the knee, which is the most commonly studied joint in sheep and goats. The procedure may be done arthroscopically if size permits. The cartilage surface is exposed and a defect is created to the desired specifications. The defect may be created with a handheld rotary drill, a low-speed motorized drill, or a curette. Care must be taken to irrigate both during the defect creation, as well as following, to minimize the risk of thermonecrosis and remove residual particulate bone and cartilage prior to device implantation. The depth of the defect should be determined based on the intended clinical application of the device.

The device should be implanted in a standard and reproducible manner. Care should be taken to ensure that the articular surface of the implanted device is flush with the surrounding articular cartilage. The implantation procedure should mirror the clinical deployment of the device as closely as possible. A standard closure should be performed following implantation and appropriate analgesia should be administered. Intra-articular injections of local anesthetics should be avoided due to concerns of possible chondrocyte toxicity. Next slide.

Postoperative rehabilitation protocols in humans usually limit immediate full weight bearing but do allow for limited flexion and extension of the joint. This immobilization can be provided in large animals but is more difficult to employ in the bilateral animal models. Complete immobilization prevents joint flexion as well as limiting weight bearing, which is not ideal and can be associated with articular cartilage degradation. Partial immobilization allows for approximately 20 degrees of joint flexion and extension which allows the animal to lie down and rise up independently while also allowing weight bearing for balance and limited ambulation.

Recovery pens should be designed to reduce stress and minimize excessive motion. Animals are initially housed in protective stalls immediately following surgery and later allowed more freedom to roam in herds. The animal should be observed frequently for signs of pain or distress and any concerning observations should immediately be reported to the study veterinarian. Next slide.

Imaging is an important part of both the clinical and preclinical evaluation of a cartilage repair device. An MRI can be performed in animals throughout the study, although this procedure does require sedation or anesthesia when performed in vivo. Because an MRI can be done in both animals and humans, the results can be compared, allowing us to gain a deeper understanding of how device performance in the animal population correlates to that in the human population. MRI evaluation of the joint or cartilage structure should evaluate articular surface integrity, thickness and volume of chondral surface, subchondral bone plate contour, thickness and volume of synovial membrane, and volume of synovial fluid. Next slide.

Although pain and mobility are best evaluated during the clinical study, the animal study allows a more thorough evaluation of device performance and safety through ex vivo analysis of the tissue with gross pathology and histopathology. Histology is used to

evaluate the local tissue response as well as monitor the device resorption and new tissue formation. Histological evaluation should include assessments of matrix zonal organization, cell density, cell morphology, collagen types and concentration, and inflammatory response. Evaluation should include the implant defect site with opposing cartilage surface, as well as the synovium. Synovial fluid samples should be evaluated, as well. Recommended stains include the standard H&E as well as safranin-O, toluidine blue, or modified trichrome. Immunohistochemical evaluations are helpful to evaluate the type of cartilage within the repair site which provides insight as to the quality of the newly repaired cartilage tissue. Histomorphometric analysis may be utilized to evaluate tissue thickness, integration, cell number, and surface quality. Next slide.

Mechanical evaluations are an important aspect of implant evaluation and should be included in all pivotal animal testing on cartilage repair devices. Mechanical testing can provide assurance of functional restoration and can serve as an index of durability. Unfortunately, mechanical testing may damage the tissue, impacting our ability to evaluate the tissue histologically. Therefore, additional animals should be included for biomechanical endpoints.

Mechanical testing should address the ability of the implant to withstand expected in vivo static and dynamic loading such as compression and shear and tension; analysis of the fixation method, such as strengths of the integration between the product and the surrounding native tissue and propensity to generate wear debris. The testing should evaluate both the static mechanical behavior of the product by measuring the maximum recoverable compressive strain, the aggregate modulus, the shear modulus and permeability, as well as the dynamic mechanical behavior of the product including an assessment of the complex shear modulus. For degradable products, these properties should be evaluated over time. Samples for these tests may consist of explanted tissue

from the animal model and should be compared to control tissue such as cartilage collected from an un-operated control joint. Next slide.

Osteoarthritis and cartilage wear is a common clinical concern for both humans as well as animals. In companion animals such as dogs or horses, severe pain secondary to osteoarthritic joints often represents a terminable diagnosis. For this reason, animal studies in veterinary clinical trials for cartilage repair products are of the utmost importance, and information collected from these studies can be mutually beneficial to both human and animal populations.

For future considerations, well-designed and well-controlled veterinary clinical trials may provide a new way to evaluate these device types in animals with naturally occurring defects which more closely mirror the human clinical condition. Translational studies such as these represent a previously untapped resource of information that may help us better realize our goal of the 3Rs. Next slide.

Bone and cartilage defect models provide a wealth of information about a device's or a product's performance; however, they are challenging models to execute correctly. In many cases, the studies provide information that cannot be obtained clinically.

We're committed to the 3Rs of refinement, reduction, and replacement and are looking forward to developments in One Health to allow veterinary trials to support performance. Regardless of the approach, we strongly recommend you discuss your plans with us in a Q-submission. Thank you for your time.

DR. MOORE: You managed to pack so much interesting material into your presentation, Dr. Miller. Thank you.

Dr. Donita Bylski-Austrow will now be presenting an overview of orthopedic scientific models for the spine. She is Research Professor Emeritus of Orthopaedic Surgery and Biomedical Engineering at the University of Cincinnati, and the former director of the

Biomechanics Laboratory at Cincinnati Children's Hospital Medical Center. She received a bachelor's degree in mechanical engineering, master's degrees in bioengineering and applied mechanics, and a Ph.D. in bioengineering from the University of Michigan.

With no further ado, Dr. Bylski-Austrow.

DR. BYLSKI-AUSTROW: Good morning. I appreciate the opportunity to be a part of this program. I'll be giving a summary of some of the spine animal models related to orthopedic products.

The range of patients and clinical problems is large, from older adults to early childhood, deformities to degeneration. The choice of a preclinical model depends, of course, on the purpose. Also, the focus here will be on adult lumbar spine fusion of the intertransverse processes, then briefly, interbody fusion and a few non-fusion models. The most common animal models are rabbit, pig, goat, sheep.

There is an FDA-recognized consensus standard that is a preclinical in vivo animal model, ASTM F3207. The purpose is to evaluate the effectiveness of products intended to cause or promote bone formation in the lumbar spine at a single level from a posterior lateral approach to the transverse processes. The animal model is the adult rabbit. The standard is important not only for the specific subject, but as an example, for development of possible future consensus standards. It covers animal demographics, surgical methods, postoperative care, and assessments of fusion by the methods listed. It does not cover GLP requirements, which are the responsibility of the sponsor.

Inclusion criteria includes species, age, weight, and closed physes. Implant mass and volume are specified. The same for control and treatment groups. Sample size is discussed, based preferably on power but a minimum *n* of 6 to 8 for all final analyses after losses. Primary outcome is fusion rate at 8 or 12 weeks. A possible secondary outcome is quantitative histomorphometry. Time points are immediate post-op and at least two time

points before the maximum time. Ethics and regulatory approvals are discussed. Surgical methods from anesthesia to approach of L5-L6. On reaching the TP, care must be taken to limit exposure of adjacent facets or TPs.

The extent of decortication of the TPs has been shown to be critical to fusion rate. Further, it is important not to extend to the vertebral body in order not to inflate fusion rates.

For the control group, iliac crest bone is harvested for autogenous graft. The location, extent, and volume are defined. Morselized bone with all soft tissues removed. Size of pieces is specified.

Decortication and graft material should be confined to the medial half of each TP. Placement of graft over the perispinal bed and adjacent TPs over the red zones is shown. Fill in between the two TPs using either iliac bone or test article.

Recovery and postoperative protocols are discussed. Pain monitoring, nutrition, and careful handling, as well as observations, especially adverse events and protocols for early deaths.

Experimental endpoints are designed to analyze new bone formation. First, necropsy, excise and save select or systemic tissues and lesions. Order of procedures begins with tissue harvest and proceeds through histology.

To assess fusion by radiography, acquire consistent clear images of the entire operated segment and at least one adjacent level on either side. Scoring is by three independent trained assessors. Left and right are scored independently, scoring is binary, fused, or not fused by given criteria. Micro-CT may be performed. Scoring is binary or morphometric parameters may be quantified.

Manual palpation is the primary biomechanical option. Ways to minimize bias, as well as personnel, timing, harvesting, embedding forces are specified. Biomechanical

testing is first uniaxial tension to determine of stiffness and ultimate load on the experimental level and to an internal control level. Multidirectional flexibility tests may also be performed for range of motion and neutral zone.

Histology and/or histomorphometry are used to determine whether there is continuous bone between the TPs, confirm living bone, evaluate maturity and quality of bone and cell and tissue responses. Embedding in section locations are discussed.

These are preferred stains. Semi-quantitative evaluations are performed by a specialized pathologist. Review all slides, all sections. A recommended histopathologic scoring system is provided, adapted from ISO standards.

Definitions of fused and unfused are shown with schematics. For fused, a calcified bone or a marrow bridge is evident between the TPs. For unfused fibrous tissue, fibrocartilage or cartilage prevent a stabilizing bridge.

For histomorphometry, analyze all slides for calcified bone and residual implant. A trained assessor is needed to differentiate the two.

Capture the entire region of interest while excluding the area occupied by the TPs. Calculate percent calcified bone and percent residual implant.

Statistical analyses. For biomechanics, express as ratio of fused to adjacent unfused level. Note required minimal descriptive statistics. For ordinals, semi-quantitative histopathologic measures, use nonparametric tests such as Kruskall-Wallis to compare multiple groups or time points. For specific comparisons, Kolmogorov-Smirnov, Wilcoxin rank-sum, or similar. Adjust for multiple comparisons. For quantitative histomorphometry, one or two-way ANOVA followed by Tukey or related.

Criteria for success is bone formation with mass sufficient to stabilize the level. Minimum evidence is fusion by palpation, implant resorption over time by histology, and lack of adverse cell responses. Supporting evidence includes radiography, biomechanical

tests, and microscopic new bone formation, if the amount is enough to carry a load, and prevent movement and implant resorption over time. Microscopic new bone formation alone does not suffice.

References for this standard include the Boden '95 studies in 60 rabbits with two negative control groups. Meta-analysis of the rabbit model showed an overall fusion success rate of 52%. Reliability was graded as excellent. Others represented relevant surgical anatomy of the rabbit lumbar spine, musculoskeletal and neurologic, and operative methods. The effect of operative technique was analyzed. There was an initial complication rate of 26% and zero after protocol refinement. Precise protocol was support for a cost-effective and accurate model.

The final reference to find the baseline kinematics of the rabbit lumbar spine showing similar ranges of motion between rabbit and human, and greater neutral zones of the rabbit. A recent review of over 800 rabbit surgeries using this model reported fusion rates at 12 weeks of 70 to 77%, and occasional complications due to self-trauma.

I'll mention one other ASTM document, "Guide for Preclinical In Vivo Evaluation of Spine Fusion." This one is not an FDA-recognized consensus, it is much more general than the one just discussed. Summaries of animal models are presented for about 300 studies of posterior, lateral, and interbody fusion.

An early review noted that the first report was canine model over a century ago. Rats to primate models were reviewed. Whereas intertransverse fusions can be performed in most species, interbody fusions require the large parallel end plates seen only in larger animals.

Moving to interbody fusion, this study is pigs and polymer scaffold cage with biologics. It was cited in a recent book chapter, "FDA Premarket Review of Orthopedic Spinal Devices." This was a two-level anterior model, two treatment groups. It presented

an elution time plot for the biologic component.

This last fusion study used goats and a two-level lumbar interbody fusion using carbon-reinforced PEEK cage.

Now moving to non-fusion. First, adult disc replacement in the lumbar spine. Two studies, both chosen because they were cited in the FDA premarket review chapter. This one used sheep and a bioactive fabric. And this one used baboons and an elastomeric total disc replacement.

One slide for pediatric non-fusion. Models have been developed to modulate vertebral growth in AIS. Two series led to FDA IDE studies: a titanium staple-screw construct in pigs, and a tether in first calves and then mini-pigs. All animals skeletally immature. For younger children, growing rods or expansion thoracoplasty are used. Models have been the larger animals for growing rods and a rabbit model for chest cage expansion.

Are quadrupeds good models for human spines? Certainly, similarities and differences exist. These are some of the studies that have considered biomechanical comparisons.

The 3Rs and validities may bear repeating, also a systematic model development process with time for strong evaluations, and critical review of some of the previous studies may help improve translation, especially those studies with no reported adverse events or high *n* with small effect.

In conclusion, an orthopedic specific animal model for spine fusion has been developed into an FDA consensus standard with ASTM. Development of new consensus standards based on related models for potential spine treatments, fusion and non-fusion, may help to clarify and streamline premarket application processes. Thank you.

DR. MOORE: Dr. Bylski-Austrow, thank you for that very informative presentation.

We will now be hearing a presentation on assessment of endpoints in animal studies. Dr. Jeremiah Easley serves as the director of the Preclinical Surgical Research Laboratory located within the Translational Medicine Institute at Colorado State University. He is a diplomat of the American College of Veterinary Surgeons with over 10 years of experience working with industry and institutional partners. His area of expertise focuses on the evaluation of orthopedic, spine, and sports medicine related medical devices and orthobiologics, utilizing both large and small translational models. Additionally, Dr. Easley's research focus is aimed at developing new large animal models that more comprehensively mimic the human orthopedic conditions.

Dr. Easley acquired his doctor of veterinary medicine degree from the Virginia-Maryland Regional College of Veterinary Medicine in Blacksburg, Virginia. He then went on to pursue large animal surgery by completing an internship at the Equine Medical Center of Ocala in Ocala, Florida. This was followed by a 3-year large animal surgical residency at the University of Florida in Gainesville, Florida.

Once again, please remember to use the OHT6-Feedback@fda.hhs.gov e-mail to send in your comments and questions.

And now, Dr. Easley.

DR. EASLEY: Hello, thank you all for joining us today. My name is Jeremiah Easley and I am a veterinary surgeon and direct the Preclinical Surgical Research Laboratory at Colorado State University. I will be presenting on assessments and endpoints in animal studies. This is a very large topic for only 10 minutes, so I will aim to speak in general terms across both large and small animal studies and address the most important points for FDA regulatory submissions.

There are numerous ways to run an animal study. No matter the method, all groups require the following team members to successfully perform an animal study. Having a

complete team that works closely with each other day in and day out will help with study efficiency and flow. The team, in general, is tasked with following a detailed study protocol, analyzing the data and creating a results package that clearly achieves the objectives set forth in the study. Every member of this team is absolutely vital to the overall study success. Most importantly, every member of this team must put the humane care and welfare of the research animal as their number one priority.

There are numerous models that could be utilized to achieve your research objectives and some models may be more appropriate than others depending on the device being tested. It's important to remember that no model is without flaws or limitations and no animal model perfectly mimics the human disease condition.

In order to increase your odds of a successful study, I recommend using a model that the researcher and facility are comfortable with and have extensive experience in, a model that provides consistent results and a model that is validated and accepted within the literature and by the regulatory agency.

In many instances, a pilot study can be very valuable to help with decisions around endpoints and outcome assessments. Additionally, cadaver trials and pilot studies serve to reduce costs and improve the ability to stick to the 3Rs of animal research. Cadaver and pilot studies utilizing a small number of animals with a short survival period could make all the difference to ensuring a successful pivotal study.

When designing a study and considering assessments and endpoints, I recommend everyone do the following: submit an FDA pre-submission. This is a really good way to initiate your conversations with the FDA and start to build a working relationship with the FDA. It's important to remember that the FDA is part of your team in this process.

Number 2: Work closely with an FDA consultant or a consulting firm. The regulatory processes required to take your device into human clinical use is challenging, stressful and

complicated. FDA consultants can help to streamline this process, keep your company on track, and help you keep your focus on the true requirements of the regulatory process.

Number 3: Strike a balance between all parties that are making decisions. There are a lot of groups involved in this process and there is no way to give them all what they want. It's important to keep your focus on the true requirements to achieve the objectives of your study.

And lastly, number 4: Keep things simple, do not overcomplicate your study, and do not try to answer too many questions. Additionally, make sure your devices are sized appropriately and instrumentation works appropriately for the animal model used.

So in summary, you start by working with your research team and FDA consultants to develop your FDA pre-submission plan. Work closely with the FDA to get the feedback and suggestions on how best to design your study and choose your outcome measures to achieve your objectives. This may be a back-and-forth process and could require multiple meetings. The study can then start and it's important to follow GLP guidelines and work closely with QA for oversight of the study.

Once the study ends, a complete package of the results can be submitted to the FDA for review. It's important to realize that following all of these steps appropriately, even in the face of positive study outcomes, does not guarantee FDA approval. The FDA may need additional information and additional studies may be required. No matter the outcome, always work with all members of the study team to answer the required questions and work closely with the FDA to ensure you are fully understanding their needs and taking every action to provide them with the information they are requesting.

When designing your study, coming up with the appropriate endpoints will depend heavily on the study objective, the device indication, and device material and the animal model utilized. The FDA typically likes to see a short and long-term endpoint, at minimum.

Short-term endpoints typically range from 4 to 8 weeks, midterm endpoints at 12 to 52 weeks, and long-term endpoints ranging from 26 to 104 weeks in most animal models. A time point earlier than 4 weeks may be requested for safety assessments to understand cellular responses prior to bony healing. But for orthopedic devices, a time point shorter than 4 weeks can confound your results because this is during a high tissue inflammatory phase, especially in large animal species.

When testing a resorbable device, the FDA may request an endpoint at which the device is fully resorbed to understand the complete immune response to that resorbable material. Typically, in orthopedic studies, as the study becomes longer, the outcomes start to converge onto one another. So having a short and long-term time point helps to tell a complete story about the product being tested in comparison to control or predicate devices. Ultimately, the study has to be financially feasible, as well, so you cannot design a study with tons of endpoints.

One way to reduce animal numbers and ultimately overall cost may be to perform in-life assessments to replace a few endpoints. There are numerous in-life assessments available, but they vary across animal species. One of the most common in-life assessments is going to be physical examination and lameness examination. Both exams are considered subjective and can be challenging to accurately perform in certain species. The horse is probably the easiest species to accurately perform a subjective lameness assessment in, while fight-or-flight animals such as sheep can be more difficult to perform such assessments in, as they can often hide subtle lameness or signs of pain.

Numerous objective gait analyses systems exist, such as treadmills, Tekscan, ANY-maze animal trackers, and accelerometers. These objective assessments can result in massive datasets over an entire study period and can help to tease out performance differences between groups.

Other in-life assessments can include blood or tissue analysis such as complete blood counts and blood chemistries. These blood tests are often taken prior to study initiation and at sacrifice. They can be utilized for assessment of overall health. However, it's important to understand that certain blood values can vary on a day-to-day basis and it can be challenging to interpret abnormal values in the absence of clinical abnormalities.

In-life imaging can be highly valuable in understanding the performance of a device at interim time points. Radiographs are frequently utilized to ensure proper implant placement or changes with an implant location over time. Radiographs often lack the resolution to assess true performance such as bony in-growth or new bone formation, especially in larger species with increases in tissue summation. CT and MRI are modalities with high spatial and contrast resolution, thus improving accuracy and reliability. Additionally, both modalities provide multiplanar imaging and 3-D reconstructions. These advanced imaging modalities, while valuable, may not be available in many research organizations due to the cost of purchasing or maintaining the equipment.

In conclusion, the benefits of these in-life assessment options should be weighed against the risks and you should ask yourself the following questions prior to including these assessments in your study:

- Are these in-life assessments truly able to answer the questions being asked?
- Are they accurate enough to not confound the overall study data?
- Are they worth the additional cost or risk to the animal?
- And in the end, do the outcomes of these analyses outweigh the ex vivo outcomes?

When performed, in-life assessments should be considered supplemental information that hopefully strengthens the overall ex vivo study outcomes.

There are numerous ex vivo assessments that can be utilized to show safety and

efficacy of an orthopedic device. The most common analysis to understand device performance are biomechanics, micro-CT, and histomorphometry. Each one of these tests adds an integral piece to the overall puzzle and should be analyzed together. Some devices may be more suitable for destructive mechanics depending on their intended indication or clinical problem the device aims to solve. Destructive mechanics will require increased sample sizes, whereas nondestructive mechanics allow samples to be used for micro-CT and histomorphometry and histopathology. In general, biomechanics will typically result in less significant differences between groups compared to micro-CT or histomorphometric outcomes.

Histopathological analysis utilizing ISO 10993-6 for local toxicity and 10993-11 for systemic toxicity are critical for understanding a device's safety. Oftentimes these analyses can be performed within the same study, while other times it may be more appropriate to perform numerous separate studies to fully prove a device's safety. Small animal models utilizing purpose-bred species that are genetically very similar and have been raised in heavily controlled environments are more ideal for systemic toxicity analysis and will likely provide more consistent and accurate results compared to large animal models.

There are additional tests at a microcellular level available, such as transcriptomics or metabolomics. But oftentimes these assessments are not a requirement of the FDA for orthopedic device assessment and can be limited to certain species only. Additionally, data from these tests can be challenging to interpret, making safety and performance outcomes somewhat open-ended and leading to further questions. I do expect these microcellular analyses to grow and become a common part of the FDA submission package in the future, as these tests become more accessible and validated to specific animals.

In summary, when designing a study and prior to study initiation, it's vital to ensure the team is qualified and all members are seeking the same objective. Most importantly, do

not forget that the FDA is a player on the team and like any successful team, it's important to involve all players. Accept that no animal model is perfect, and that is okay. Numerous animal models may be required to truly answer all questions. It's better to perform numerous simple and straightforward studies than it is to overcomplicate a single study with confounding results. Thank you, and have a good day.

DR. MOORE: Thank you for sharing your expertise with us, Dr. Easley. It's much appreciated.

The next presentation will focus on clinical translation. Dr. Matthew Allen has held the professorship in small animal surgery at the University of Cambridge since 2014. At Cambridge, he directs the Surgical Discovery Center which focuses on preclinical and clinical translational studies in orthopedics, and is the Director of Clinical Research at the Queen's Veterinary School Hospital. His areas of research focus include orthopedic animal models, comparative musculoskeletal oncology, surgical navigation, and surgical robotics.

Prior to Cambridge, Dr. Allen was Associate Professor of Small Animal Surgery at the College of Veterinary Medicine, The Ohio State University, from 2008 to 2014 and Assistant Associate Professor of Orthopedic Surgery at SUNY Upstate Medical University in Syracuse, New York, from 1996 to 2008. Dr. Allen has a veterinary degree, a Ph.D. in comparative orthopedics, and a bachelor's degree in pathology, all from the University of Cambridge.

Just a quick reminder, please remember to use the OHT6-Feedback@fda.hhs.gov e-mail to send in your comments and questions.

Over to you, Dr. Allen.

DR. ALLEN: Good morning. It's a great pleasure to be able to talk to you this morning about clinical translation and the role of veterinary clinical trials in the development of orthopedic products.

By way of background, we've already heard from this session that preclinical animals

provide fundamental data on the safety of therapy, materials, and devices. Many of the early studies for materials and devices involved the implantation of small amounts of material in sort of a pure form, not necessarily fabricated into a functioning device but more as a test implantable device. Cylinders, etc. Sheaths, etc. And those can provide fundamentally useful information about the safety of the material itself. But when it comes to the actual use of a device, typically there's a pivotal animal study that involves what we call a simulated use model.

But in all of these situations, whether the pivotal study or the earlier studies, the animals that we're using for these preclinical data collections have normal tissues, they have no preexisting pathology. And that's really important, of course, because that allows us to make an association between the surgery and the implantation of this test device and resulting pathology. And with appropriate controls, operator controls, etc., predicate controls, we can tease out what is device specific and therefore what may be cause for concern or in fact, evidence for safety.

Now, veterinary clinical trials provide an invaluable option for translating new therapies and devices into patients and they are much more of a real-world look, if you like, at how these devices will perform. This presentation is going to overview, from a fairly high level, the pros and cons of veterinary clinical trials and briefly discuss the regulatory oversight of such work.

So what are the advantages then of veterinary clinical trials? So many of the clinically important musculoskeletal diseases seen in humans are also seen in companion animals, and a good example of those would include arthritis, which we see often post-traumatic osteoarthritis in the dog rather than primary idiopathic osteoarthritis. We see bone cancer, most especially canine equivalence of pediatric bone cancer, so malignant bone tumors seen in young animals recapitulating almost exactly the biology of the disease

seen in children and young adults with primary bone tumors such as osteosarcoma. We see osteomyelitis within the context of fracture, for example, but also within the context of the use of implantable devices, so as a complication of surgery. We also see intervertebral disc disease in dogs and that can be very useful, both in terms of assessing functional recovery of neurological function but also, of course, of assessing and treating pain.

Relative to preclinical healthy animals, veterinary clinical patients often have significant comorbidities that more closely mimic the situation in human patients that are being treated. And so there can be existing pathology but, of course, also there may well be concurrent treatment with therapy so there may be other medications being given and those again could be more representative of what happens in people.

We have an advantage, as well now, particularly in the last 10 or 15 years, to the tremendous growth in our ability to track and follow up our animals using imaging, biological biomarkers, and then some validated clinical outcomes measures is really improving our ability to get quantitative information of response to therapy, both from a veterinary clinical trials setting but also just in terms of straightforward veterinary medicine and following our patients up and looking at now an audit of our clinical performance.

This all really comes under the umbrella of One Health and One Medicine. And so this is not new. Back in the 19th century, Virchow, the famous Virchow of Virchow's triad, was saying, "Between animal and human medicine there is no dividing line—nor should there be." This idea that the information we get from trials in animals can be used to inform the care of animals and the care of humans is really fundamental, I think, to the way that veterinary medicine is evolving. Certainly, within the academic environment there's a tremendous emphasis on developing ways that we can translate information, not just from the bench to the bedside, but also from the beside to stall side into our veterinary patients. So I think a really important thing to recognize is there is a growing interest in the use of

veterinary clinical trials as a way of doing this, so developing this One Health/One Medicine approach.

Whenever there's a slide set that has advantages on it, there's always going to be a disadvantages slide set, as well, so we may as well deal with this now. There are a number of disadvantages to doing clinical trials. None of them is an absolute obstruction to doing them, however. They're inconvenient, they are annoying and they can be costly, and they most importantly need thinking about, but these are absolutely not reasons not to do them.

Firstly, they can be very hard to run, mainly because, in contrast to calling Charles River up and ordering 16 New Zealand white rabbits between three and a half and 3.8 k, we get what comes in the clinic door. And so it can take a while, depending on the frequency of the disease condition, can take a while to accrue these cases. And not everybody who you see who has a pet with one of these conditions wants to enroll in a clinical trial, so we have fallout at that point, as well.

Even when we can recruit the patients into our clinical trials as subjects, we have much more limited options for invasive tissue collections. These are pets, they're owned, privately owned animals, and from both an ethical and also social constraints, meaning that we are not likely to be able to go and do very invasive tissue collections on them after we've done our therapy or implanted our device.

Sometimes you're able to get end-of-life commitments from the owner but usually, with relatively young animals, that's a long time in the future and it's not that helpful. You might be able to get serial blood samples, you certainly can get imaging, but beyond that it can be very tricky and that really speaks to the challenges then in getting good safety data. Often, we'll talk to clients about the fact that the best we get out of these clinical trials is really an absence of toxicity. But frankly, all of that absence of toxicity information should have been developed before we get into the veterinary clinical trial anyway, so really they

don't add much. What they're really looking at is efficacy, feasibility, within a patient population.

We have limited, or some would say no control over the care of the animals in the context of a private home, so once those animals leave your facility and go home, you've got absolutely no control over the drug dosing, the rehab protocols, etc. So this is really important to have a client education program that makes sure that clients understand that, because we are dependent on the owner to bring the patient back for follow-up. It's not, again, the same as walking out to the animal surgery because you know it's 4 weeks and the bunnies need an X-ray. You have to hope that Mrs. Smith is bringing her dog back in at 4 weeks and hasn't forgotten.

We'll often use financial incentives to try and offset the cost of fuel or the cost of travel in general to try and make this happen, to encourage owners to come back. But those financial incentives can themselves be challenging from an ethical perspective.

Most significantly, I think, when you're thinking about veterinary clinical trials, is the fact that you have to recognize that we are not dealing with a homogeneous population of animals. We'll have differences in demographics, disease state, and comorbidities that can really complicate the interpretation of a treatment response and make the sample size calculations that we've used pre-clinically pretty irrelevant. So it's very important to recognize this isn't just for this.

It is also important to recognize it's the PI, that you have a lot more regulatory noncompliance potential, there are more moving parts and more opportunities for miscommunication between yourself and the owner with regard to care of the animal. And at the end of the day, the owners are able to remove their animals from a study at any point without any explanation, if they see fit, and that can obviously degrade your sample numbers and affect your statistical power. But you cannot control it, again, except by good

communication skills with the client.

So how is this overseen then? Well, in the setting of the U.S., the USDA has primary oversight of the use of animals in research within the U.S. and they delegate that responsibility down to local IACUCs and then provide oversight of those IACUCs through visits, etc.

There are complexities whenever you do clinical research in animals that goes beyond standard of care, and by standard of care, I mean a procedure that you would do in any animal with the same condition. So if you've got a dog with a tumor and you ordinarily would repeat biopsy after it's had treatment, then you could do that in the context of a clinical trial without any significant issues, with just appropriate local ethics approval from the veterinary hospital.

If, though, you're going to go in and do a whole bunch more tissue collections or collect a lot more tissue on each occasion, or you want to do something particularly unusual, some sort of advanced imaging that requires general anesthesia and risk to the animal, then you're going to require IACUC approval on top of that. And that can get quite tricky. And the USDA has generally walked away from getting too far involved with that and delegated that to the IACUCs.

So I just want to show you the sort of algorithm, the sort of flowchart that we use at Ohio State for doing this and again, this issue of what standard of care is was really central. So if the procedures are all standard of care, then local oversight by the ethics committee at the vet school was sufficient. But if there were procedures being done or the timing of those procedures was being changed simply to meet a research need, then there was going to need to be IACUC oversight.

So what could we do then in the clinical setting? Well, with regard to imaging, we can deploy a full range of things and I've just illustrated four of them here. On the left,

arthroscopy of the elbow joint, we can use that as a diagnostic tool, we can use it as a therapeutic intervention to deliver intra-articular devices or treatments. We can use standard plain-film X-ray. In this case, this is a knee replacement patient, a clinical patient of mine that had a knee replacement and a femoral osteotomy at the same time, and you could imagine that clinical cases like this could be used for looking at materials or fixation strategies for total joints or you could be looking at anti-infection strategies with coated fracture repair plates, for example. You could imagine all sorts of things. These patients are out there and available, and X-rays are a very robust and straightforward imaging modality.

Slightly more complicated, but very much more available now than it used to be, CT and MRI, the volumetric imaging can also be done and can provide tremendous information and potentially, by looking at these, you can get information and relate these back to the same imaging done in the preclinical models and try and define a relationship between imaging and, for example, tissue-level pathology, healing, inflammation, etc.

We are fortunate in our facility to have an instrumented treadmill that is extremely good, can give us outputs on limb use within about 30 seconds of completing the recording, so it takes about 10 minutes to get the full gait analysis profile on a dog. Very useful for looking particularly at staging disease to start with and then also for, of course, looking at treatment response in an objective manner. We've used this in a number of clinical trials.

Increasingly within the veterinary field we are seeing the evolution of, in our case, owner-reported outcome measures, what we call OROMs, which are very similar to the PROMs or the patient-reported outcome measures used in human medicine, so the SF-36 and the KOOS. These are equivalents to that. This is an instrument developed at Liverpool University for dogs with arthritis, called the Load. That looks at quality of life associated with disease. And on the right then is the Canine Brief Pain Inventory developed at U. Penn,

looking specifically at pain. And there are a number of others, Helsinki Pain Index, etc., looking at quality of life, functional recovery and pain. They can be very, very useful and provide the owners with an opportunity to get engaged in the assessment process.

And just to wrap up this talk, what I wanted to do is show you one of these examples in action. And so this is not a company I'm involved with in any way, I have no affiliation with this organization or the research group. I bring this up simply as a nice illustration of how one might start thinking about veterinary clinical trials.

And so this was a study where researchers and a company developed interleukin-10, which is an anti-inflammatory cytokine, it's a potential therapeutic to knock down inflammation in the context of arthritis. So they did a significant amount of preclinical work, a lot of preclinical work under GLP, to develop the safety data and toxicology data to make sure they understood dosing and safety. And they then went on and got approval to do a study in companion animals, in dogs with naturally occurring osteoarthritis, and they used this therapy under that mechanism in a veterinary clinical trial.

And using the sorts of measures we've shown earlier, in this case, range of motion as a surrogate for pain and also functional disability, you can see in these graphs that the treatment with either the low or the high dose of IL-10 plasmid led to measureable and statistically significant improvements in both range of motion and reductions in functional disability.

So this is the sort of study design and the sort of study approach that I think is really the future for these translational veterinary clinical trials. They can be extremely informative and although logistically complex and slow, especially if the case is limited, they can be extremely valuable as a guide to what's likely to happen in a human clinical trial, but also in their own right as a way of delivering potential veterinary therapeutics and devices. They are not a substitute for good preliminary safety, PK, PD, studies that inform on

infective dosing and safety. But they do offer real-world clinical relevance and potential for advances in veterinary and human health care under the One Health umbrella.

Important to recognize that sample size calculations are not going to be the same for these induced -- for naturally occurring diseases, they are induced disease models and you must account for this in your study design and outcome measures. They're not always going to be predictive, so validation of the test model is going to be critical in terms of making this relevant to humans. But there's increasing interest, especially amongst the general public, for the development of clinical trials as an alternative to induced animal models whenever possible.

That said, we feel that pressure, we hear that pressure from our clients, we understand the need for these. But it is very, very important that there needs to be robust safety data ahead even of veterinary clinical trials. So just because we're doing it in veterinary patients rather than human patients doesn't get rid of the need for really good, solid safety data. It's not an alternative to safety data, it's simply a bridge to allow us to take safety data and limited efficacy data from these as these are artificial models and bridge that towards the clinic, whether human or veterinary.

Thank you very much for your time. I'll be happy to take questions at the of the session.

DR. MOORE: Thank you for sharing this informative and interesting presentation, Dr. Allen.

So I want to say thank you to all the Session 1 presenters. We will now begin our first question and answer session. We welcome our Session 1 presenters: Dr. Fortier, Dr. Cook, Dr. Bylski-Austrow, Dr. Liza Fisher, Dr. Easley, and Dr. Allen. And they will be joined by a moderator, Dr. Sara Thompson. Dr. Thompson is a veterinary medical officer for the Division of Restorative, Repair and Fracture Fixation Devices in the Office of Orthopedic

Devices, OHT 6. She jointed FDA/CDRH as an animal study reviewer specializing in the assessment of animal models and nonclinical animal testing for orthopedic devices. Prior to joining FDA, Sara was a clinical veterinarian focusing on small animal emergency and critical care. She graduated from the University of the South with a B.S. in biology and received her doctorate in veterinary medicine from Texas A&M University.

To the audience, please remember to use the OHT6-Feedback@fda.hhs.gov e-mail to send in your comments and questions.

And I'll turn it over to you, Dr. Thompson.

DR. THOMPSON: Thank you. I'm ready to go ahead and start with the first question. This one is for Dr. Cook. Could you please outline how you validate your preclinical models for your studies?

DR. COOK: Oh, thanks. Great question. I definitely appreciate getting to tease that critical point out a little bit more. So while the classical statistical measures of validity are super important, of course, and always part of the equation, when I'm talking about a valid model, I'm referring to producing evidence that the model has similar symptomatic, functional, diagnostic, and therapeutic characteristics to what you're after, what's the target problem being investigated. So does the lesion cause pain and lameness? Does the defect have the kind of signs that we'd see in the target population, patient population? And then the other part of that is, does that problem, does that defect deficiency pathology resolve on its own or not?

So to me then, there are three ways to validate a model. It may be validated already, check ASTM, check consensus statements; organizations sometimes will put those out or definitely the peer-reviewed literature. Secondly, then, as I outlined in the talk, that's really one of the main purposes for pilot studies, so validating that in terms of what we're talking about, does the model do what we're intending it to do. And then kind of like

what Matthew just talked about, it may be well described in veterinary patients. So if we can use a spontaneous, naturally occurring model, then check the veterinary literature and discuss with veterinarians, as well.

DR. THOMPSON: Thank you. This one kind of piggybacks off of that validated model idea. This one is for Dr. Fisher, who is sitting in for Dr. Miller because she had a conflict. The question is regarding sort of the size of the bone defect. What data is there to support the critical-sized defect that has less than 10% healing over the course of the study? How is that model validated given that there is a lot of, sort of -- tends to be some conflicting information in the literature?

DR. FISHER: Yes. Thank you, Sara. So the recommendation for this less-than-10% bone formation in a critical-sized defect over time comes from a publication, and this shows the importance of using a negative control to demonstrate improved performance of the subject device, bone void filler as compared to an MT defect. We typically see this MT defect included in the animal studies we review and the model does produce less than 10% bone formation over time. Using fully grown, skeletally mature animals is recommended as well, because using young rabbits, for example, might result in seeing more bone growth than anticipated. We also would recommend that an experienced veterinarian, ideally one experienced specifically in orthopedics, should be conducting the studies.

DR. THOMPSON: Thank you, that was helpful information.

This one can go to maybe Dr. Easley, but I think anybody can chime in as well on some of these more general questions. When do you recommend using micro or regular CT scans to assess healing?

DR. EASLEY: Yeah, great question. So obviously, micro-CT is going to have higher resolution, you can get down to smaller slice thicknesses and have much greater resolution on smaller sample sizes. There's obviously limitations between what you can actually -- the

size of implants or the size of bones that you can place in the micro-CT units, as well. So a lot of the difference is going to be based off of what you're trying to analyze and then obviously, the size of the specimen. You know, I typically use CT imaging for larger specimens and also for specimens that I'm trying to get an overall picture of what's going on and that might be if you take, let's say if we were to do a posterior lateral fusion in a sheep, you're not going to be able to use that functional spinal unit and place it into a micro-CT unit in most scenarios.

So you can get an overview of what the fusion mass looks like in a CT unit and then still get a smaller, more higher resolution analysis using micro-CT of that same specimen, to get more analysis in regards to the details or the bony structure within that region of interest. Does that hopefully answer the question there? But that's what I would -- that's how I decide for the use of both and I think that -- I don't think that it's an "and/or" scenario, I think you could do both in the same model and get different information across the board there for using both of those.

DR. THOMPSON: I have a follow-up question on that. The imaging is frequently seen or primarily seen at the terminal endpoint time points. What do you think some of the challenges of limitations that we don't see as much in, in vivo imaging with these animal studies?

DR. EASLEY: Yeah, so it is certainly hard to truly replace a time point with some form of in vivo imaging. While we understand to some degree what the outcomes are for imaging, whether it be CT or MRI and looking at different types of signals of bone or radio densities, it's certainly not going to be a replacement in many scenarios for something like histopathology or histomorphometry. With that being said, it does allow you to follow the progression of changes over time nicely and in some scenarios that's going to be the best option because you can't have studies that are so large that they're financially not able to

be performed. So I think that it's a good alternative. The limitations are still going to be that you may not be able to truly link what's happening on CT or MRI or radiographs to what you would expect on histomorphometry or histology or mechanics, even. So it is something that we certainly understand what images -- you know, the findings in these types of imaging modalities, what they allude to, but they may not be as definitive or most of the time they're not going to be as definitive as those ex vivo analyses. So that's the limitation, but I don't think that it means that you don't use them, I think that it means that it's supplemental information that really strengthens your overall outcomes in the end.

DR. THOMPSON: Thank you. The next question is for Dr. Allen. You mentioned in your presentation that there is not so much oversight for veterinary clinical trials at this time with no real central authority. How does this more localized approach to oversight impact the data integrity and what might be some future considerations to mitigate this challenge?

DR. ALLEN: I think you have to be careful of making too broad a statement, it depends where you are in the world. I mean, the U.S. situation is very, very different from the UK situation where there's extremely tight control over it. I guess what my perspective would be, because I believe that veterinary clinical trials are going to be an important thing for the future in terms of leveraging these data both for human benefit but also for our patients, that we need to have more of a focus on how we better regulate them because, exactly as you say, if you don't have good oversight you've got questions over data integrity, compliance, ethics, etc.

So in the UK, we've just being going through a series of panels at the Royal College to try and develop better guidance for how we deal with these sort of studies that fall into the gray areas. They are challenging, and we need guidance from regulatory authorities and the people charged with particularly the legal aspects of this to make sure we stay compliant,

because to not make use of these existing clinical caseloads, I think, is to our detriment and certainly to our future patients' detriment.

DR. THOMPSON: Thank you. This one is for Dr. Cook. Or really anyone. Again, these can be -- anybody can chime in. There have been lots of comments on developing new ASTM standards for models in cartilage and spine. The development and validation of new models can be very expensive. Are there funding opportunities available for development of these standards and has anyone had much success acquiring this funding?

DR. COOK: Great question, difficult one. I mean, I think there are potentials for that. Those are hard to get. In my mind, those are probably best suited for organizations like -- and subcomponents of organizations like the preclinical animal models group of ORS where, as a collaborative team, you can leverage funding which may then come back to industry, especially if this is going to benefit industry in the long run, in terms of having a known pathway to getting things approved safely and efficaciously. At the end of the day they can definitely benefit from having a template, right? And so I think we have to think beyond our governmental funding sources and foundational funding sources and think about organizations leveraging that.

And I think I'm a big believer that teams always defeat individuals, so I think you got to get multiple institutions to come together and say like, listen, we're the power players, here's what it's going to do to benefit you and then try and leverage, especially industry funding, would be my best bet for that.

You know, a lot of people have done bootstraps approaches and come up with consensus statements and I think that can be helpful, but that's on your dime and your time and so you just got to be willing to do it for the greater good, which a lot of people are, especially on this panel and this in group, so that's another way to do it, on the bootstrap.

DR. THOMPSON: Thanks, there are definitely lots of challenges there.

This one is for Dr. Bylski-Austrow. Several of your examples of interbody fusion are performed at two vertebral levels. What are the pros and cons of using a two-level model as opposed to a single-level model?

DR. BYLSKI-AUSTROW: Yeah, there are many between one level and two level, and the consensus standard is a one-level model and in the academic literature there are not consensus standards, there are a variety of approaches taken. So it would depend on exactly what problem you're trying to approach. And the simpler, the better/the least complex, the better unless it's absolutely necessary and if it's necessary, then it's necessary. That's all I would say.

DR. THOMPSON: Thank you. Dr. Easley, you emphasized -- and really all of you, again. You emphasized the importance of pilot studies in the product development process. Can you describe a situation which a pilot study will yield useful information for the design of the pivotal study?

DR. EASLEY: Yeah, that's a great question. I typically like to use meniscal studies as a really good example for that. There are lots of different models or types of devices that you would look at. I mean, every one of them really would be helpful in regards to doing some, definitely, cadaveric work and then some pilot work in most scenarios.

But meniscal studies are a really good example where you might be doing a meniscal replacement or a meniscal repair that obviously that tissue is very challenging to work in, the model in general can be challenging, and we've seen where you could do the procedure but within a month of the procedure being performed, you might have a product that's -- you know, the surgical procedure is not ideal for the specific animal, the animal is noncompliant in regards to making sure that the implant stays in place, things like that, where a small pilot study that lasts 1 month in a small group of animals to ensure that those types of details are worked out before moving to a pivotal study are really good examples

of where that would come in handy versus you design a study where you go "let's go 12 months out in a meniscal study to analyze healing" and then realize that the device didn't stay in place or didn't perform the way it should have within that first month. To me, pilot studies are integral to ensuring outcomes that -- you may not always ensure outcomes of the device performance, but you're certainly going to rule out problems in regards to procedural issues or issues that, let's say the device just doesn't work well with that species or in the sizing of that animal and things like that.

DR. THOMPSON: Thank you. Yeah, pilot studies are definitely helpful at reducing animal numbers and making studies count.

This one is for Dr. Allen. Are there challenges with connecting medical device startup companies that are designing the devices with the facilities, like the veterinary centers that would potentially be carrying out veterinary clinical trials? And if so, what are some ways to overcome those challenges?

DR. ALLEN: I think it comes back again to what Lisa said in the first presentation, really, which is to -- and again, what Jimmy identified, I think probably what we've all said, which is at some point or beyond, talk to a veterinarian. If you talk to a veterinarian, veterinarians will connect you, a good veterinarian is going to connect you with his or her network and make recommendations. The institutional veterinarian, despite the fact that they work within the constraints of an institution and focus presumably on live animal medicine, is a veterinarian, and these individuals are highly trained, highly connected, and they understand the local environment around them and can make recommendations.

So the veterinary fraternity again, as was suggested, things like the preclinical model section of ORS, there is sort of a network already built there of people who are doing this sort of work, who know people who do this sort of work. Maybe there's not complete overlap between the people doing clinical trials and the people doing ORS-level preclinical

safety data, for example, but those individuals know each other and I think that's the way forward, is to make sure. And I would say that, more generally, in the context of One Health/One Medicine there's an opportunity here for much greater coordination of efforts between medicine and veterinary medicine, to make sure that we do the right thing for all of our patients. So I think, as I say, it is mostly communications.

There is certainly no lack of enthusiasm for clinicians to do the best for their patients, whether they're human or veterinary. So there are challenges, and it's good to talk to somebody who's done this. But any one of us on this call can come up with a list of 10 people who do this, who are absolute world experts at getting these studies done, and we're always willing to share opinions. That's never a weakness in a veterinarian.

DR. THOMPSON: Thank you, that's a real good answer.

I think that we are approaching our time, so we'll wrap up the panel discussion and I'll turn it back to Dr. Moore to wrap things up. Thank you, again.

DR. MOORE: Thank you. Thanks to all of you for virtually participating and for posing some great questions and providing some fantastic answers.

We're now going to take a 10-minute break, so we'll resume the meeting at -- let's go with 10:46 a.m. And please remember to use the OHT6-Feedback@fda.hhs.gov e-mail to send in any comments or questions that you may have. Thanks.

(Off the record at 10:37 a.m.)

(On the record at 10:46 a.m.)

DR. MOORE: Welcome back. We will now hear the perspective of regulatory staff. We are joined by our first presenter, Aric Kaiser, who is a biomedical engineer with experience in tissue mechanics and mechanical testing. His scientific and regulatory interests are in the design and evaluation of products intended to treat orthopedic disorders, in particular tissue-engineered medical products, which are combination

products, and devices intended to serve as functional replacements for diseased or damaged tissue. He has been involved in various aspects of orthopedic biomechanics ranging from implant design and testing, to hard and soft tissue characterization for over 30 years. Since 1994 he has been a regulatory review scientist at FDA where he has been involved in the development of guidance and other regulatory activities that have supported the advancement of new technologies for replacing damaged orthopedic tissues, all this while ensuring patient protection and sensible regulatory oversight.

Mr. Kaiser, the floor is yours.

MR. KAISER: We heard in the earlier presentations that there are a variety of animal models that people have investigated over the years. Some of these are validated, some have been used by numerous researchers and others only by the group that developed them. Regardless of the status, there's always the possibility that each group that implements a given model will do so in a different way. In order to reduce or remove these differences in implementation, it's necessary to provide standards for guidelines.

What I'm going to do is highlight the methods that FDA uses to try to organize and standardize the various animal models that exist. We do this by the use of standards and guidance. Standards are prepared by outside organizations and they have input from FDA. In contrast, guidance is written by FDA with input from outside organizations.

Why are standards important? As I already mentioned, different groups can have different interpretations in implementation of a given model or test method. Standards allow for creation of a well-defined method or set of information by a group of stakeholders that have an interest in that model or test method. The end result is a document that was formed by consensus and describes an agreed-upon set of information.

While FDA believes that participation in standards activities is important, it's also a legal requirement. The National Technology Transfer Advancement Act enacted in 1996

mandated that federal agencies use consensus standards in meeting their agency's legally defined objectives. It also encouraged agencies to participate in the creation of standards that are relevant to their activities.

Having mandated agency use and participation of standards activities, from a legal standpoint, what is a standard? The NTTAA includes a definition and, as you can see from these excerpts from the law, it pretty much matches up what a standard would commonly be considered to be. It's a document that codifies rules, test methods, processes, definitions and activities, among other things. This allows different groups at different locations in time to work from a common set of conditions.

In order to be considered a consensus standard, NTTAA outlines the conditions that must be present in the development process. These are also the conditions that standards development organizations follow. A consensus standard must be developed in an open environment where anyone with an interest can participate, must contain a balance of opinions, must be developed under a set of established rules where all participants are equal, must have an appeal process built into the development process and finally, it must be developed using a consensus process. If any of these attributes are not present in the standard development process, the resulting document is not a consensus standard.

As I indicated earlier, the definition of a standard, NTTAA identified the types of things that we typically associate with a standard. In practice, we see standards for many things as outlined by this list of examples. In orthopedics we commonly see standards that describe material specifications, test methods, and specified performance. For the purposes of this workshop we can also have standards that describe animal models.

Now that we know what standards are and how they're created, how does FDA use them? Standards can be adopted into law, they can be incorporated into regulations, they can be reference and guidance documents, and they can be recognized and used by

manufacturers in support of marketing. I want to add a little more to this last point.

In the 1997 FDA Modernization Act, FDA was tasked with creating a database of standards that we would recognize. What this means is that we would identify standards that we agree with. If a manufacturer stated that they comply with the contents of the standard, we wouldn't need to review the details of the information derived from the standard because we already knew how they were generated or what they said. The advantage is that this can reduce review time.

Several times during the year, FDA reviews new or modified standards and makes a judgment with respect to our level of agreement in whole, in part, or not at all. We publish a database on our website that lists the recognized standards. While manufacturers aren't required to only use FDA-recognized standards in their marketing submissions, their use can streamline the regulatory process. I want to emphasize this last point.

Use of standards by a manufacturer is voluntary. They don't replace requirements outlined by law or regulation, but their use may satisfy a legal or regulatory requirement. It can't satisfy all the requirements in a marketing application, but they may be used to provide a significant amount of information used in the regulatory process. So that was from the manufacturer's side.

The last thing I want to describe is how FDA uses standards. Aside from the recognition database, we have to determine the applicability of a given standard to a given use. While standards can provide useful information and create standardized descriptions of things and test methods, as well as potentially reduce review times, it can't solve all of our problems, they need to be applied judiciously.

Having outlined what standards are and how useful they can be, I have to describe reality. With respect to orthopedic animal models, there really aren't that many standards that we have access to. I'm going to show you three ASTM standards, but only two of these

still exist, one of them was withdrawn recently, leaving us with only two active standards applicable to animal models. Of these, only one of them actually describes an actual animal model. The other one is essentially a summary of relevant literature related to an animal model, but not a description of how to actually implement the model.

The first standard is ASTM F2451, this is the one that I mentioned that has been withdrawn. So this standard, while it did describe some information relevant to evaluating products for cartilage repair, is no longer available for use.

The second standard, ASTM F2721, is intended to provide a summary of literature describing models that people have developed over the years for evaluating segmental bone defects. This standard still exists and it's still referenced by numerous companies when they're evaluating products intended to fill bone defects.

The final standard, ASTM F3207, this is a standard that actually describes a model, it goes into fairly extensive detail as far as how the model is defined, the surgical techniques, the way the data get collected and evaluated, and has become a very useful standard for our evaluation of bone products intended for posterior lateral spine fusion.

Back to the discussion of standards. The other activity FDA has for standardizing and organizing information is the guidance document. This is the method that we use to present our current thinking on a given topic, we create these. Guidance can be written so that it applies to every type of medical product. An example of this is the biocompatibility guidance. Or it can be written so that it only applies to a specific product. An example of this would be the PMA guidance. Guidance creation is governed by good guidance practices. Most guidances are written by FDA, published in draft form in the *Federal Register*, where we seek comments from the public, rewritten based on those comments, and then published in final form in the *Federal Register*. It is important to appreciate that while we refer manufacturers to guidance in order to understand our position on a

particular topic, the information in guidance documents isn't legally binding, it's simply a recommendation.

There are currently three guidance documents that relate to orthopedic animal models. Two have been published in final form and the third is currently available in draft. The oldest guidance document applies to bone void fillers. It outlines in general terms the types of information that we prefer to see in a bone void filler 510(k). For those manufacturers that are active in this area, you'll have noticed that the level of information we provide to you during more recent discussions is more detailed than what you find in the existing guidance. This exemplifies how guidance can become outdated as FDA and manufacturers learn more about a particular device over time.

The second guidance we have is a joint guidance created by CDRH and CBER that applies to products intended for cartilage repair or replacement. It provides a high-level set of points to consider when designing bench, animal, and clinical studies for these types of products.

The last guidance is a draft, and like the cartilage guidance, outlines general principles; in this case, those that would be applicable to any animal study. Because it's currently in draft form, it can't be referenced or implemented yet.

Now that you know what standards and guidance are and how they get used, you can see that they can be extremely helpful in all phases of the regulatory process. You can also see that there's a lot more work that can be done to create more standards and guidance related to orthopedic animal models. While the focus of this meeting is on animal models, there are certainly times when non-animal models, standards, and guidance are also appropriate. We encourage sponsors to consult with us if they wish to use a non-animal testing method they believe is suitable, adequate, validated, and feasible. We'll consider whether such an alternative method could be assessed for equivalency to an

existing animal test method.

When considering the number of animals and the amount of data that can support the safety and performance of a medical device, FDA recommends balancing the ethical principles of the 3Rs: reduction, replacement, refinement, as well as regulatory least-burdensome principles with the goal of using the minimum number of animals necessary to generate valid scientific data to demonstrate reasonable safety and performance.

DR. MOORE: Thank you for sharing your insight and these important considerations, Mr. Kaiser.

Our next presenter is Dr. Annabelle Crusan, she is a veterinary medical officer at the Office of Product Evaluation and Quality in CDRH since 2015. She conducts animal study reviews from protocol development to final reports, and serves as a subject matter expert for GLP compliance field investigations. She serves as FDA technical contact for ISO 10993 Part 2, animal welfare requirements; Part 6, local implantation; and Part 11, systemic toxicity; the accreditation scheme for conformity assessment; ASCA reviewer; and as a member of the FDA animal welfare subcommittee; FDA alternative methods working group; and ICCVAM metrics working group.

She works on revision of guidance documents that involve animal studies and international standards, such as bone and soft tissue implantations. Annabelle is also a laboratory animal veterinarian. She has directed an animal program and has performed numerous works on different animal models and devices prior to joining FDA. She has co-authored peer-reviewed articles, white papers, and a book chapter on animal models, alternatives, and animal welfare.

Just a quick reminder, please remember to use the OHT6Feedback@fda.hhs.gov e-mail to send in your comments and questions.

And now Dr. Crusan.

DR. CRUSAN: Hello, everyone. Hope you are in best of health. As I was introduced, my name is Annabelle Crusan. I am a laboratory animal veterinarian and a veterinary medical officer at CDRH. From 2016 to 2020, I had the wonderful opportunity to review animal studies for the Office of Orthopedic Devices. I feel grateful to be presenting to you today about a topic I am passionate about.

For the next 20 minutes I am going to give you an overview of good laboratory practice regulations for animal studies to evaluate safety of medical devices in terms of fundamentals of GLP and where our animal study recommendations and feedback in the nonclinical safety assessment of medical devices come from. I will also share perspectives on the study design, 3Rs, conduct, and reporting animal studies for demonstrating reasonable safety of a medical device to support clinical trials and marketing submissions.

We have five topics to cover. We will look at the big picture first. The GLP for preclinical or premarket safety study basics. Then I will slightly touch on the regulatory applications of 3Rs, or replace, reduce, and refine, otherwise known as the Russell and Burch's Principles of Humane Experimental Technique. Then we will review the current regulatory requirements. I will then proceed to how animal studies reviewer identifies regulatory and safety issues during animal studies review. And then I will give you examples of common animal study integrity and quality issues and safety deficiencies I have identified repeatedly from submissions, to give you a sense of how to mitigate these potential deficiencies for consideration, for maintaining quality and integrity, and streamlining your next animal study.

Twenty-one C.F.R. Part 58, otherwise known as the GLP regulation, describes good laboratory practices for conducting nonclinical safety studies. Compliance with this part is intended to ensure the quality and integrity of the safety data. The purpose of the GLP studies is to evaluate the safety of the device prior to first use in people, therefore

protecting public health. GLP studies can be used to satisfy part of the requirements of a new device to enter the market, and regulatory decisions are based on valid scientific evidence providing reasonable assurance that the device is safe, effective, and reliable.

There are Class II and Class III devices that require GLP animal safety studies prior to first in human. Specifically, I am talking about the large animal studies where we deliver, deploy, or implant the device.

I wanted to note that in our 2020 biocompatibility guidance and in our EFS program, safety experiments should be conducted in accordance with the recognized GLP regulations. If any such study was not conducted in compliance with GLP, a statement detailing how the study complies with each part of GLP regulations must be provided with an explanation of how, without an independent audit, the Agency can be assured that all of the data reported in the results represent all data obtained.

Moreover, such a study can be used to support an early feasibility study IDE application only if the deviations from GLP are identified and justified, and do not compromise the validity of the study results. Additional GLP animal study data may be needed to support a larger clinical study with the final device design.

Using animals as surrogate models for a complex biological system like human in testing medical device safety realized in the conjecture that animal models predict the human outcome. Still, animal models are not perfect. However, we at FDA have received and reviewed numerous and diverse animal data that give us some level of confidence with regards to the reliability of animal models we review in addressing safety endpoints in spite of the model limitations. FDA supports the principles of the 3Rs to reduce, refine, and replace animal use in testing when feasible.

We encourage sponsors to consult with us if they wish to use an alternative method. However, for large implantation studies, alternatives to demonstrate the safety of medical

devices in animals may not be feasible. A GLP study offers advantages over a clinical trial because it has the ability to follow animals during in-life phase of the study, having controlled environment, feed, water, to minimize the variability and confounding effects, daily health assessments, ability to perform intermittent procedures, and unlike clinical trials, animal enrollees are not lost to follow-up. There is also an ability to conduct a full pathological evaluation in each study animal and other specialized studies done postmortem, such as biomechanical testing.

How do we use animal studies for safety information? The main purpose of an animal study is to evaluate device safety, which includes assessment of device functionality, performance in handling, biological and physiological compatibility, toxicity, and effectiveness in vivo. As I mentioned, animal studies allow for postmortem evaluation, inform endpoints for a clinical trial, provide a better understanding of host device interactions and in rare cases, may augment the need for clinical data. A GLP study is for the demonstration of reasonable assurance of safety.

The GLP study design is driven by the indications for use statement. FDA pays close attention to the indications for use or IFU statement proposed by sponsors because we expect nonclinical studies to address all components of the IFU for future labeling requirements. The study design is also driven by simulation of the clinical setting so that it reflects the intended use and proposed labeling of the device. For instance, the simulation of the surgical procedure up to the postoperative care by treatment of the animal in ICU or critical care setting. Study design is also driven by the device class. Lastly, the study design is driven by the primary safety endpoints. Through CDRH's pre-submission program, we can discuss experimental designs that support greater measurement precision and can improve the signal-to-noise ratio of the analysis.

I mentioned that we will go briefly over the 3Rs, the guiding principles for the ethical

use of animals in testing. I included a lot of information in the next two slides, but we will not go on a deep dive into them today as it demands a whole separate presentation by itself. However, the information I put in here is to assert that there is an existence of many regulatory applications of the 3Rs at CDRH and use of the 3Rs through good laboratory practice.

In this slide, I wanted to underscore that GLP promotes the reliability and reproducibility of the test data and hence, facilitates the international acceptability, such as the U.S. participation in the OECD mutual acceptance of data, reducing the need for repeating an animal study, eliminating redundancy, and reduce the waste from biased results. The elements of GLP are constant and they collectively establish a quality system for animal care, data quality and integrity, that benefits animals in the study. FDA is fully committed to complying with rules and guidance governing animal research and wellbeing of research animals. The assessment of animal research also includes consideration for the availability of acceptable alternatives.

The Animal Welfare Act and regulations require institutions and principal investigators to consider discomfort and pain to animals and assure pain and discomfort is limited to that which is unavoidable while conducting scientifically valuable research. The AUR (ph.) also require documentation ensuring alternatives were considered. The PHS policy requires assuring institutions to avoid or minimize discomfort, pain, and distress when consistent with scientific practice, use the minimum number of animals necessary, and consider the use of in vitro and non-animal models. It is also important to note animal research is not ethical if it does not generate value for science and society, therefore the robustness of each study should be a large part of the continuing conversation and research goals. Studies using animals still underscores the current requirement to provide data supporting first in human trials in marketing for medical devices. Animal experiments, by

their very nature and purpose, will cause pain, suffering, and distress, and in many cases, the death of the study animal. Morally and ethically, it's critical to minimize these harms and to undertake these studies as humanely as possible. Humane and high-quality animal studies can result in reduction and refinement. Reduction and refinement need to be considered whenever the use of animals to achieve a scientific objective is deemed unavoidable.

In combination with the Animal Welfare Act and regulations and PHS policy, the GLP section on animal care, Part 58.90, promotes better health status that can reduce the numbers of animals needed to obtain data of the required quality. It is also possible that in some circumstances, GLP can be the only regulation that can cover the care and use of mice and rats bred for research, species that we often see in biocompatibility studies.

I see good laboratory practices as an opportunity for refinement because it is an adoption of best practice in a quality system. We emphasize on the good quality, good quality animal care that foster positive welfare. Good laboratory practices inherently results in good quality safety data from the animals and in doing so, can benefit the care and welfare of the animals during the GLP study.

In 1980, Dr. Paul Lepore of the Bureau of Veterinary Medicine of the Food and Drug Administration stated in a publication that GLP was enacted in response to the appalling circumstances uncovered in a limited series of inspections of laboratories that was performed in the 1970s. One of the appalling findings was improper laboratory animal care and procedures, therefore GLP was instituted. Now, this sets the stage to talk about the current regulatory requirements of GLP and why it is a quality system that ensures the safety and integrity of the animal data and ensuring regulatory compliance.

The FDA published GLP final rule through the *Federal Register* in 1970 and on June 20th, 1979, the FDA enacted all aspects of its GLP program. Congress mandated FDA

to develop and implement agency-wide bioresearch monitoring program in GLP. Because of the FDA field inspection operation between 1972 to 1974 findings, FDA found careless experimentation, improperly trained employees, un-reviewed data, omitted data, improper laboratory and animal care procedures, and improperly monitored contract studies including the failure of sponsors to validate the data appearing in the final study reports.

You may be familiar with the information in this slide, the 10 subpart aspects of the GLP regulation. As you can see, the 1978 final order on GLP, including the preamble, is still applicable today. During its enactment, it is hoped that these regulations will increase public confidence in FDA decision making and will make sure that safe products are approved for marketing.

Personnel should clearly understand the function they perform and has to be assured by the testing facility management. A scientist or other professional of appropriate education, training, and experience shall be identified as a study director. An effective, active QAU is crucial for ensuring data quality and that attention paid to day-to-day quality assurance activities will foster regulatory compliance.

The attending veterinarian is not mentioned in GLP regulations yet plays a significant role in GLP studies. In our 2010 animal study guidance, FDA recommends that you initiate early and frequent dialogue with attending veterinarian about ways to detect and eliminate clinical and subclinical disease to ensure optimal animal wellness.

Facilities should have suitable size and construction for activities, segregated areas, animal housing, and supply facilities. Equipment should have appropriate function, design, and capacity to conduct studies. Best facilities operations should include written SOPs including animal care, housing and identification, food and water analysis, bedding, and best control appropriate to prevent confounds.

For TA/CA, identity, strength, purity, composition, other characteristics are required.

Reserves from each batch should be maintained in studies for more than 4 weeks. Ensure proper handling and storage and stability testing before and during the study.

Each GLP animal study shall have an approved, written protocol that clearly indicates the objectives and all methods for the conduct of the study. I listed here the protocol requirements.

GLP study shall be conducted in accordance with the protocol with the animals monitored in conformity with the protocol. Wise (ph.) integrity and quality. Data integrity is the degree to which data are complete, consistent, accurate, trustworthy, and reliable over the life cycle of data.

Data quality, on the other hand, is generated according to applicable standards and have characteristics that allow it to be used as intended that includes appropriate study design that accurately and scientifically addresses the experimental question and hypotheses tested.

Expect data to be of quality and integrity through use of ALCOA+ or attributable, legible, contemporaneous, original, accurate, plus complete, consistent, enduring, and available.

Here I listed the final report for GLP requirements. The final report shall be signed and dated by study director after which any changes to report to request amendment and reason documented.

As we have highlighted earlier, GLP is a quality system concerned with the organizational process and the conditions under which animal safety studies are planned, performed, monitored, recorded, archived, and reported to FDA. All raw data, documents, protocols, final reports, specimens, shall be maintained in archive for prescribed times. Archives must be orderly, indexed with limited access, prevents deterioration and shall be overseen by responsible individual.

When reviewing the final report, I wanted to be able to reconstruct the animal study. The report should be able to describe what happened to each individual animal from receipt into the test facility to in-life, and postmarket evaluation and to the archival storage of their tissues.

When I review animal studies, I keep the printed regulations handy. I compare protocol versus final report, I ask whether all required elements are present, including amendments and deviations. I also compare final report versus raw data. Does identification appear adequate? Is reporting on articles and test systems adequate and consistent?

And with regards to the final report versus images, I compare images to the final report and I ask are images identified by test system, study nature, date of collection, and any accompanying documentation. And do images support observation and outcomes in the final report?

The primary value and reason for QAU audits, if done properly for all phases of the study, is that the audits provide assurance to FDA that the study was conducted against the approved protocol and any deviations from the protocol were reported to the study director and test facility management.

One of the major problems discovered back in the '70s was no protocols were used or if there was a protocol, it was rudimentary, and scientists just kept revising and changing procedures and was not scientifically rigorous by any stretch of the imagination. An effective, active QAU is crucial for ensuring data quality and that attention paid to day-to-day quality assurance activities will foster regulatory compliance.

Here are the common data quality and integrity issues I see in animal studies reviews: lack of QAU; inadequate personal background, knowledge, and training; protocol deviations; omissions of methods, records, and reports; discrepancies and inconsistencies;

study design-related concerns.

Common animal study deficiencies. The device is not the final finished version; study design not appropriate for the device or too few animals per cohort; inadequate discussion of adverse events; lack of detail in the study reports; incomplete animal study data; attachments not included; study report rewritten by a company representative rather than the study director; publication or a poor synopsis in the study report and draft reports.

To recap, we touch on the GLP regulations, regulatory applications of 3Rs. We reviewed the current regulatory requirements, we identified regulatory issues during animal study review. I gave you examples of common animal study deficiencies that can impact safety review and can impact the quality and integrity of safety studies.

The takeaway message here is that regulations under 21 C.F.R. Part 58 establish a quality system for animal safety studies to ensure medical devices are safe prior to human testing and that studies are humane, of good quality, and are retrospectively re-constructible and reproducible.

I included this slide on helpful references that I also referred to for this talk.

I wanted to acknowledge my colleagues at OHT 6 and FDA colleagues in preparation for this presentation. And thank you, everyone, for being so gracious with your attention.

DR. MOORE: Thank you for sharing this presentation with us, Dr. Crusan.

Our next presenter is Dr. Sara Thompson, a veterinarian medical officer for the Division of Restorative, Repair and Fracture Fixation Devices in the Office of Orthopaedic Devices, also known as OHT 6. She joined FDA as an animal study reviewer specializing in the assessment of animal models and nonclinical animal testing for orthopedic devices. Prior to joining FDA, Sara was a clinical veterinarian focusing on small animal emergency and critical care. She graduated from the University of the South with a B.S. in biology and received her doctorate in veterinarian medicine from Texas A&M University.

Just in case you've forgotten, please remember to use the OHT6Feedback@fda.hhs.gov e-mail to send in your comments and questions.

Over to you, Dr. Thompson.

DR. THOMPSON: Hello, and thank you for participating in the animal studies workshop today. I am Sara Thompson and I am a veterinary medical officer for the Office of Orthopedic Devices within the CDRH. Today I will provide a high-level overview of the review of animal studies.

Please note that this presentation is not intended to provide prescriptive guidelines on animal study design. Rather, my intention is to provide insight into the animal study review process, including specific considerations that are unique to the evaluation of orthopedic devices.

Additionally, we encourage sponsors to consult with us if they wish to use a non-animal testing method that they believe is suitable, adequate, validated, and feasible. We will consider such an alternative method could be assessed for equivalency to an animal test method.

When considering the number of animals and the amount of data that can support the safety and performance of a medical device, FDA recommends balancing the ethical principles of reductions, replacement, refinement, as well as regulatory least-burdensome principles with the goal of using the minimum number of animals necessary to generate valid scientific data to demonstrate reasonable safety and performance.

As a veterinary medical officer at CDRH, one of my primary job responsibilities is evaluating the adequacy of animal study data that is provided in support of marketing applications. Robust animal study data is an integral part of the evaluation of device safety and performance, often serving as a surrogate for clinical data. The objective of my presentation today is to provide a regulatory perspective on animal study reviews focusing

on study design considerations specific to orthopedic devices. I will highlight some of the considerations specific to the animal models discussed in the first half of the workshop, including extremities, spine, and soft tissue. For the purposes of this presentation, I will be using the terms "device" and "product" interchangeably. However, the term "product" applies specifically to medical devices that also include a biologic or a drug.

The Medical Device User Fee Amendments implemented the broader Q-submission program, also called the Q-sub program, which includes pre-submissions as well as additional opportunities to engage with the FDA. Those opportunities include obtaining feedback on premarket approvals, humanitarian device exemptions, de novo requests, and premarket notification or 510(k) submissions, as well as addressing whether a clinical study requires submission of an investigational device exemption. The Agency strongly recommends that applicants submit a draft of their animal study protocols prior to initiating any in vivo animal testing.

The pre-submission program provides an excellent opportunity to obtain FDA feedback on specific questions to guide product development and submission preparation. Early interaction with FDA staff is encouraged to determine what type of preclinical testing will be needed to support a future marketing application. If we determine that in vivo animal testing is required, we can provide guidance on those study designs. The pre-submission feedback is most effective when requested prior to the execution of planned animal testing. There is no fee associated with these submissions.

For additional details about the Q-submission program, please consult the guidance for industry and FDA staff, "Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program." The link is listed on the bottom of the side.

Preclinical animal testing provides an initial assessment of how the device interacts with biologic systems and also how the biologic system may affect the device. FDA's

primary purpose in recommending animal testing is for the applicant to provide evidence of safety, including performance and handling. A secondary objective is to evaluate the effectiveness of the device or to demonstrate proof of contact. Because the primary purpose of the study is to evaluate safety and performance, a risk analysis should always be performed prior to initiation of the study.

The study objectives should be designed to evaluate all identified risks of the device, as well as any known risk of the device type. Sometimes these objectives can be accomplished in a single pivotal study. However, more often than not, additional studies are necessary to adequately address all of the identified risks.

The topic for today's workshop is functional animal studies. Functional animal studies are designed to evaluate device performance and handling. Biocompatibility evaluations are also an important aspect of evaluating device safety. However, the testing described in ISO 10993 would not be adequate to evaluate device performance.

Depending on the product, animal data alone can support the safety and effectiveness of the product. However, in other instances it serves as supporting data to initiate a clinical study where both the animal and clinical data support the product's performance for a marketing submission.

Regulation governing good laboratory practices, 21 C.F.R. Part 58, was enacted in the 1970s to help labs produce reliable data with a goal of data integrity. Any animal studies intended to support the safety of a medical device or a combination product should be conducted in accordance with recognized GLP regulations. If a study was not conducted in compliance with Part 58, a statement should be provided explaining the reasons why the study was not GLP compliant, including a detailed discussion on any deviations from the regulations.

Perhaps one of the most important study design considerations is a choice of the

animal model. The animal model should be representative of the indications for use and emulate, as much as possible, the morphology, histology, biomechanics, and kinetics corresponding to its human use.

The choice of animal species is usually dictated by the objectives of the animal study. Smaller animals, such as rabbits, are usually more appropriate for proof of concept studies or initial dosing studies. The anatomy of large animals, such as sheep and goats, more closely reflect that of human anatomy, allowing for preclinical testing which more closely simulates clinical conditions. Because the bones of adult sheep and goats are similar in size and composition to humans, these species are ideal for evaluation of orthopedic devices. Larger animals are more appropriate for pivotal animal studies which require a functional animal model.

When choosing an animal model, first consider whether there is an established animal model for the type of device being tested. An established animal model is one that has been described in the literature or used to support the clearance or approval of a similar device for the same indications for use. Often, an established model does not exist, particularly with novel device types or devices whose identified risks cannot be mitigated with the existing models.

The animal and its physiologic attributes should provide a test system that simulates the clinical setting as closely as possible. For a functional animal study, consideration should be given to how closely the surgical technique and the method of implantation can be replicated. For example, differences in anatomy of the knee joint between sheep and humans often necessitates modification of many surgical procedures in order to access the joint space. We must also consider how the animal ambulates and the biomechanical forces placed on the test system following implantation. How do those forces differ in a quadruped as opposed to the bipedal human? The animal chosen should be sufficiently

large to adequately investigate and optimize the formulation, design, dimensions, and associated instrumentation envisioned for human use.

Because there are often several iterations of a test article prior to the initiation of a clinical study, we recommend that pivotal animal studies utilize test articles that represent the final clinical design. Whenever possible, the tested device should be the final, sterilized, ready-to-be-implanted version of the device, including any associated hardware.

However, differences in anatomy and biomechanics may necessitate modifications to the device itself or to the implantation procedure. For example, the subject device may need to be scaled down to facilitate implantation due to size differences between most animal models and humans. In dosing studies, the concentration of the biologic or drug are adjusted in order to determine the most effective dose with the least adverse effects. Appropriate justification should be provided for any modifications made to the device or the test system.

Animal testing should involve the worst-case construct of the total system. Worst-case represents a set of conditions that reflect the greatest challenge to product integrity and safety which might occur during clinical use.

The number of animals and experimental grouping should be designed following pilot and bench testing, which can provide some idea of reliability and outcome. It is important to utilize sufficient animal numbers to obtain predictive outcomes. However, we recommend using the smallest number of animals that will provide meaningful interpretation of the data. We urge you to be mindful of the 3Rs: refinement, reduction, and replacement, when considering the number of animals required for animal testing. Although the animal testing described in ISO 10993 is not adequate to support device performance, an applicant can incorporate biocompatibility endpoints into the performance study in order to reduce the number of animals requiring sacrifice. For example, local tissue

toxicity may be evaluated using ISO 10993-6 during a performance study that uses a critical defect model to evaluate the performance of a bone graft substitute. However, the performance of a bone graft substitute should not be evaluated using the bone implantation tests method described in ISO 10993-6 Annex C. Through the Q-submission program, the Agency can provide valuable feedback on the appropriateness of the animal model prior to the initiation of the animal studies.

When you are evaluating the performance of a device intended for use in an adult population, the animals chosen for investigation should be skeletally mature. Because weight charts can give a premature indication of skeletal maturing, radiography to document closure of the tibial growth plates should be performed to confirm skeletal maturity prior to implantation. Alternatively, the animals included in the study are old enough to guarantee maturity, such as rabbits greater than 9 months old or sheep greater than 3 years.

The device design and intended use should be used to inform the study groupings for animal testing. If the animal testing will be leveraged for systemic endpoints, the device should not be implanted in the same animals that will be used as the control. Appropriate control groups should be selected. Comparator groups are often representative of the current standard of care, such as autograft. Alternatively, they may represent a previously cleared or approved medical device with similar material composition, technological characteristics, and indications for use.

A negative control will help characterize the effects of the procedure itself and ensure that the model was executed properly. Missing or inadequate controls add uncertainty to our conclusions about the study, so we recommend you discuss these with us in a Q-sub.

Evaluation time points should be chosen with consideration for the device material

composition, the length of implantation, and the rate of degradation when applicable. In most animal studies, a minimum of three evaluation time points is recommended. The earliest time point will allow for an assessment of the initial biologic responses to the device. An intermediate time point should establish interim device behavior between earlier and later time points, as well as document or reduction of any initial inflammatory response.

For resorbable devices, the final time point should be of sufficient duration to demonstrate bone and tissue healing and to characterize the effects of any residual device material. It is understood that the final time point may not allow for complete device resorption. However, the compilation of all the time points should demonstrate a trend towards complete device resorption. Additional time points may be needed to allow for a more complete assessment of the biologic response and characterization of device components at relevant times.

The study end points are usually determined by the study objectives. We are not seeking the same data from an early feasibility study that we might look for in a safety study. A study focusing on safety might not have the same endpoints as a study that also looks at the performance of the device. Even within a biocompatibility study, we would expect much different endpoints for a study assessing systemic toxicity than one that only assesses the local effects.

Endpoints tend to be divided into two groups, although there is some overlap. Typical in vivo endpoints include clinical observations such as physical exams, gait analysis, lameness assessment, and pain scores; clinical pathology, arthroscopy and arthrocentesis, as well as imaging. Typical ex vivo endpoints include imaging, gross pathology, histology, histomorphometry, and biomechanical testing. Additional endpoints might also be considered for an infection model. The Agency can provide feedback on the animal study

design and the animal study endpoints through the Q-submission process.

I would like to take a moment to touch on some of the animal models that are commonly used to evaluate the safety and performance of orthopedic devices. A critical-sized defect model can be used to evaluate the performance of bone graft substitutes such as calcium salt bone void fillers.

It is important to note that there are differences in the purpose and parameters evaluated in animal performance testing. Therefore, the bone implantation study described in ISO 10993-6 Annex C cannot be leveraged for animal performance testing endpoints. However, a study using a critical defect model may be leveraged to support biocompatibility endpoints such as local tissue response.

The most common critical defect model that we review is the rabbit femoral defect model. However, a critical defect model can be performed in other animals such as sheep, goats, or canines, or in other bones such as the tibia, the humerus, or the scapula.

A smaller animal such as a rat or a mouse would not be appropriate to evaluate bone graft substitutes due to differences in bone metabolism that allow them to experience continuous bone growth throughout their lifetime.

In the femoral defect model, a cylindrical defect is created in the lateral femoral condyle starting at the cortical shell and extending into the underlying cancellous bone. A critical-sized defect will not spontaneously heal during the lifetime of the animal and is typically characterized by less than 10% bony regeneration.

The dimensions of critical defects differ between species and should be based on documented evidence from literature. For example, a rabbit critical defect may be defined as 6 mm in diameter and 10 mm deep, while a sheep critical defect would be much larger, measuring closer to 10 mm diameter and 13 mm deep. Because there is no clear consensus on the exact dimensions of critical defect sizing, it is important to include prospective

concurrent negative controlled defects, also known as MT defects, which verify that the model has been properly implemented. Segmental defects may also be used to represent critical defect models; however, they typically require augmentation with hardware.

Studies evaluating bone graft substitutes intended for use in the posterolateral spine are typically performed using the single-level rabbit posterolateral or intertransverse lumbar spine fusion model, which was developed by Dr. Scott Boden and is detailed in ASTM F3207. A larger animal, such as the sheep, may be acceptable, but the smallest animal model that should be utilized is the rabbit.

Multiple test materials should not be implanted in the same animal, such as a new device on one side and autologous bone graft control on the other side at the same spinal level because this prevents assessment of bilateral fusion and creates the potential for interactions between the different grafting materials. The tested graft materials should include the bone graft substitute being investigated; a comparator device, such as legally marketed predicate device; and an autograft control. The use of autograft as an internal positive control is important to evaluate whether the model has been properly implemented.

The graft material should be placed bilaterally, not unilaterally, to emulate clinical use of the resorbable bone graft substitute. For the rabbit model, the most commonly fused levels are L4-L5 and L5-L6. The transverse processes should be decorticated with extension of the decortication to the lamella, but the vertebral bodies, including pars interarticularis, should not be decorticated. The graft material should not be placed too far laterally so as not to inhibit fusion results. In other words, the grafting material should be located within the medial one-half to one-third of the transverse processes.

Baseline radiographs in anterior/posterior positioning should be performed immediately post-implantation to confirm graft placement. Evaluation of fusion status or

the existence of bilateral fusion as evidenced by the presence of continuous bridging bone from one transverse process to another at both graft sites should be performed using imaging such as radiographs or micro-CT, histology, and histomorphometry. Assessments of fusion should use a binomial scoring system of fused and not fused. The mechanical stability of the fusion mat (ph.) should be evaluated using either manual palpation or multi-plane stiffness or range of motion testing.

It should be noted that destructive mechanical assessment such as tensile testing to failure is not recommended. Determination of progression of bilateral fusion and device resorption requires comprehensive evaluation of all assessments, radiographs, mechanical stability, and histology.

Cartilage defect models are important for preclinical evaluation of the biologic response to investigational products intended for the repair of cartilage. A cylindrical defect is created in the femoral condyle or trochlea. The defect should be critically sized such that it will not spontaneously heal during the animal's lifetime. The depth of the lesion may vary depending on the product being evaluated and its intended use. However, most lesions should be full thickness chondral defects.

The species should be selected after careful consideration of the model's ability to reflect the intended clinical use. The joint size and load, age and skeletal maturity of the various animal models should be compared. While rabbits may be used for the initial proof of concept studies of cartilage repair products, pivotal studies should be done in animals that are sufficiently large enough to translate to the human clinical condition. Animals commonly encountered for cartilage defect studies include sheep, goats, canines, and horses. The goat model is commonly used because their cartilage is slightly thicker than the sheep, making it more closely resemble that of the human cartilage. The progression of the cartilage repair may be evaluated in vivo at intervals throughout the course of the study

using methods that mimic human clinical trials, including imaging such as radiographs or MRI and kinematic analysis.

Generally, studies that are a minimum of 1 year in length are recommended to provide an adequate period for completion of healing. This duration is also generally sufficient to allow assessment of durability of the therapeutic response and of the integrity of the product. Mechanical testing should always be included in addition to the traditional ex vivo endpoints of histology, histomorphometry, imaging, and gross pathology.

Additional details about the evaluation endpoints specific to cartilage repair devices can be found in ASTM F2451-05: "Standard Guide for in vivo Assessment of Implantable Devices Intended to Repair or Regenerate Articular Cartilage."

Often, animal study endpoints such as gross pathology or histopathology, can provide information that cannot be easily obtained in the clinical setting. For example, we usually collect histopathology data from each animal during preclinical studies; however, during clinical studies, we have no way to obtain histology samples aside from arthroscopic second-look procedures. In addition, animal testing is designed to minimize inherent variability between study subjects, allowing for an unbiased assessment of device safety and performance. This degree of standardization across each study grouping is impractical to obtain in clinical studies.

While there are many advantages of animal testing, there are some limitations. As I explained previously, differences in anatomy and biomechanics represent one limitation of the animal model. Large animal models such as the sheep and the goat provide a reasonably close approximation of the biomechanical load to humans. However, they are quadruped animals which have an inherently different distribution of the mechanical forces than the bipedal human. Any outstanding concerns about device performance due to differences in mechanical loading between quadrupeds and humans would need to be

addressed through clinical data.

In addition, replicating disease processes such as osteoarthritis, degenerative disc disease, or neoplasia in study animals represents unique challenges. Therefore, most animal studies are completed using healthy, skeletally mature adult animals. Even if the disease process can be induced, such as an osteoporotic animal model, the lab animals would not share comorbidities, such as cardiovascular disease or diabetes that might be present in a similar population of humans.

When the device associated risk cannot be adequately mitigated due to the limitations of the animal model, clinical data may be necessary to further characterize the device's safety and performance prior to clearing or approving the product for marketing.

In summary, because each medical device or product often presents a unique set of risks, there is no one-size-fits-all approach to animal study design. Through the Q-submission program, the Agency can help guide you through these challenges, particularly when discussions with FDA are initiated early in the device development process.

I have listed some helpful FDA guidance documents, as well as some FDA-recognized standards that are helpful resources when designing functional animal studies for orthopedic devices. Thank you for your time and attention today.

DR. MOORE: Thank you for sharing your insight with us, Dr. Thompson.

Our next presenter is Dr. Liza Fisher, a veterinary medical officer on the Extra-Columnar Spinal Devices Team in the Office of Orthopedic Devices. She received a bachelor of science in animal sciences from the University of Maryland, followed by a Doctor of Veterinarian Medicine degree from The Ohio State University. Prior to graduating, she spent time doing research at the National Institutes of Health and The Ohio State Department of Veterinary Biosciences. After finishing veterinary school, Dr. Fisher completed a 1-year rotating internship in small animal medicine and surgery at Friendship

Hospital for Animals in Washington D.C. Prior to joining the FDA, she has been working primarily as an emergency veterinarian in veterinary referral hospitals.

And now, Dr. Fisher.

DR. FISHER: Good afternoon. I am Liza Fisher, a veterinary medical officer in the Division of Spinal Devices, Office of Health Technology 6 in the Office of Orthopedic Devices. My talk today will review the specific animal study items that should be included in a regulatory submission with an emphasis on how to provide information and the level of detail recommended.

In this presentation, I will discuss how to provide animal performance information in a premarket submission. I will discuss the components of a complete animal study protocol and test report, and will provide consideration to assist in the presentation of animal performance data for premarket review.

We encourage sponsors to consult with us if they wish to use a non-animal testing method that they believe is suitable, adequate, validated, and feasible. We will consider if such an alternative method can be assessed for equivalency to an animal test method.

When considering the number of animals and the amount of data that can support the safety and performance of a medical device, FDA recommends balancing the ethical principles of reduction, replacement, refinement, as well as regulatory least-burdensome principles with the goal of using the minimum number of animals necessary to generate to valid scientific data to demonstrate reasonable safety and performance.

In your submission, please provide a copy of IACUC, Institutional Animal Care and Use Committee, protocol and amendments. The IACUC protocol helps us to know how many animals were approved for the study. The final report should include an animal study protocol signed by all parties prior to initiation of the study. Having a protocol that is finalized and agreeable to all parties prior to enrollment is important for data integrity.

Without this, the protocol can be changed throughout the course of the study, potentially masking any problems that might occur.

A complete animal study report should include information about the animal model and rationale for its selection, the number of animals at each time point, identification and critical specifications of test and control devices, detailed description of the surgical technique, images, scores, and test results from all evaluations for each animal, the results, interpretation of results, and conclusion.

A submission should include a signed study director's final report. Deviations from the study protocol and facility SOPs should all be listed clearly. If any changes were made as a result of a deviation, these changes should be described and justified. In this report, please include a GLP compliance statement.

Preclinical animal studies intended to support the safety and effectiveness of a medical device for marketing submissions should be conducted as per 21 C.F.R. 58, Good Laboratory Practice for Nonclinical Laboratory Studies. We believe that valid scientific evidence of reasonable assurance of safety of a device can be obtained from a well-controlled GLP animal study. The regulation contains an initial scope that covers applications for research use and those that are intended to support marketing applications.

The submission should also include a signed quality assurance unit report that meets the guidance provided by 21 C.F.R. Part 58.35 for each preclinical study. Please ensure that the methods, lines of reporting of the QAU, and periodicity of inspection of in-life and postmortem data by the QAU reports are detailed. The results should include preoperative, operative, and postoperative methods of assessment, as well as contributing scientists' reports from key study personnel, including the veterinarian. Additional information about the animal study protocol and results will be provided in the following slides.

FDA recommends careful consideration of the animal model chosen for all preclinical safety studies. The animal model should be representative of the indication for use, taking into consideration the morphology, histology, biomechanics and kinetics, as compared to a human situation. Please include a rationale for the animal model chosen, including support from literature references. Please provide the age, sex, breed, and weight of the animals in your submission. When describing the animals enrolled in the study, please include information about the study of the animals, methods of identification, and environmental housing and husbandry methods. Your report should state the total number of animals from each test group, as well as any spare animals designated to each time point.

As mentioned previously, the IACUC protocol helps us to know how many animals were approved for the study. The number of animals used must be justified, such as through performance of a sample size calculation or an estimate based on pilot studies. We recommend the preclinical animal testing be performed using the minimum number of animals required to achieve the scientific objectives.

The tested device should be the final, sterilized, ready-to-be-implanted version of the device. In your animal study report, please include the critical specifications and rationale for the device tested, including mass or volume, size, and configuration of device implanted in the study. If the final device design was not used in your animal study, you should identify all differences between the tested device and the final device design and explain how the differences could affect study outcomes. Additionally, you should justify why the final clinical device design presents no new risks to the patient as compared to the design evaluated in the animal study.

If a single device version is used to support a range of device versions, please include a justification for why the test article represents the worst-case construct. Worst-case is a set of conditions that represents the greatest challenge to product integrity and safety

which might occur during clinical use.

The control group offers a mechanism to compare your device's performance and to ensure that the model was properly executed. The appropriate control articles may vary depending on the subject device and the type of regulatory submission. In your submission, please include a description of all control articles included in the study. If you are comparing to legally marketed devices, please identify the comparator device as well as any differences between the test article and the legally marketed device. Additionally, depending on the type of device, a negative control group or a positive control group may need to be included in the animal study design.

Standard of care, such as autograft, can serve as a control group in some studies but should be clearly described in your submission. Your animal study report should include a detailed description of the surgical technique and device or graft placement. Please note that diagrams and images can be helpful.

A complete procedural protocol as well as procedural reports and anesthesia logs from each animal should be provided in the study submission. Monitoring, during and after the procedure, should address any procedural risks.

Please include a plan for any early mortality animals in your study protocol. All early mortality animals should receive the same after life procedures as the scheduled terminations, including clinical pathology, when possible, prior to termination; a full necropsy by a trained veterinary pathologist; and histology of organs and device site.

Assessments and evaluations provide key information for understanding the animal study. Animal studies can include both biocompatibility and performance endpoints. Your final animal study report should include the results of all in vivo and postmortem evaluations. This may encompass preoperative, intraoperative, and postoperative assessments, such as individual animal examinations, imaging, pathology results,

histomorphometry, and mechanical testing. Your report should include a complete presentation of all data at each evaluation time point in an appropriate format. Representative images are helpful, but prevent a complete review of the data and do not allow us to understand the conclusions. Additional details are provided in the following slides.

Ensuring that the animals are behaving normally and have no abnormal exam findings is important to demonstrate safety of a device. Please include a complete physical examination, including body weights by a veterinarian prior to initiating the study, as well as at regular time points during the study including pre- and postoperatively. Animals should also be observed daily by trained veterinary technicians to ensure that no adverse events are occurring. The protocol should also include to whom these adverse events are reported, as well as the steps or treatments taken to remedy them.

Comprehensive, systematic necropsies should be performed on all study animals at their scheduled termination or in cases of early mortality by a veterinary pathologist. This necropsy should include evaluation of all major organ systems. A full necropsy report should be completed and included with the submission. High-quality, color, digital macro- and microphotographs should accompany the board certified veterinary pathologist report.

The final report should include properly labeled and identified representative gross images collected from each section. Full color, high-quality photos should be taken of all device sites and surrounding tissue as well as any lesions noted. The purpose of the images is to provide supporting photo documentation of the pathologist's observations and narratives. Radiographic or micro-CT imaging are commonly utilized in orthopedic animal studies. In your animal study report, please include images from each animal at each time point in addition to the imaging narrative, such as a radiology report. When presenting radiographic data, radiographic images should be identified by anatomic orientation and

should focus on the implantation site.

To facilitate visualization of the results, symbols or markers should be used to highlight key features such as bone opposition, bone fusion, or device material. When using micro-CT to provide 3-D detail, please include the following: a description of the micro-CT instrument including the system model and any calibration performed; image acquisition procedures including sample preparation, scanning medium, and scan parameters; a description of the image processing procedures including selection of a volume of interest, image filtration, image segmentation, and correction or reduction of image artifacts; for any quantitative analysis, a description of the image analysis procedure, including the metrics assessed and the algorithms used.

Histologic analysis is used to provide an analysis of the types of tissues present and confirm the presence of bone and residual implant. A full histopathology report from a board certified veterinary pathologist, including all images, should be included with the submission.

When presenting histology data, please include properly labeled and stained photomicrographs of tissue samples collected from each section using both low and high magnification. Each photomicrograph image should include defined symbols that clearly highlight critical structures and areas of interest. The margins of the specimen should be marked and described in the sections examined. These histologic images should be presented in color with appropriate labels that identify the magnification power, a defect area if applicable, new bone formation, surrounding bone, test and control articles, and the different cell types present. The number of sections per animal and their location should be explicitly identified. The overall region of interest and the location within this region for all magnified views should be identified. Your report should include a description characterizing the histopathological changes such as fibrosis, inflammation,

neovascularization, and presence of device material. Semiquantitative scoring systems, such as ISO 10993-6, may be used to evaluate any tissue effects and should be described in the evaluation report.

Histomorphometry is used to provide a quantitative assessment of the extent of bone formation and measurement of the amount of graft material remaining over time. Histomorphometric analysis can be performed using manual measurements or automated. When presenting histomorphometry data, please describe the method or process used to distinguish new bone, host bone, fibrous tissue, residual implant, and void space on histomorphometry images. The region of interest should be clearly defined and exclude any area of host bone. Please include a full set of images showing the ROI along with tables reporting the values for each animal.

In addition to a thorough explanation of the methodology used and the data obtained, the report should include an interpretation of the findings and a discussion of the results. When presenting report conclusions, please include interpretation of data obtained from in vivo assessments, as well as imaging, histology, histomorphometry, and mechanical testing. This may include comments from a veterinary radiologist regarding the radiographic images or from a veterinary pathologist regarding the histology slide images.

The discussion of results should summarize how the data satisfied the study objectives and whether the study results met any predefined acceptability criteria. The discussion should also contain an explanation of how the results support the safety and/or performance of the subject device. Lastly, please conclude as to whether there was agreement between various methods of assessment, such as when evaluating new bone formation through imaging, histology and histomorphometry.

Displayed on the slide below are several references. These may also serve as useful resources when preparing a premarket submission. Thank you for listening to my

presentation. Please contact me with any questions or concerns.

DR. MOORE: Thank you for sharing this presentation and your insight with us, Dr. Fisher.

Our next presenter is Dr. Pooja Panigrahi, who obtained her undergraduate and master's degrees in material science and engineering from Northwestern University and a Ph.D. in bioengineering from Clemson University. She joined FDA in 2015 as a biomedical engineer/lead reviewer and currently serves as a team lead in the Division of Restorative, Repair and Trauma Devices in the Office of Health Technology 6 in FDA's Center for Devices and Radiological Health.

Once again, please remember, use the OHT6-Feedback@fda.hhs.gov e-mail to send in any comments and questions.

Dr. Panigrahi, the floor is yours.

DR. PANIGRAHI: Thank you. Animal studies provide important evidence for the safety and effectiveness evaluation of medical devices during their translation from design to final products. Today I will present a regulatory perspective on the role of animal data in marketing submissions.

Additionally, although my presentation will focus on the role of animal data in marketing submissions, please note that when considering the number of animals and the amount of data that can support the safety and performance of a medical device, FDA recommends balancing the ethical principles of reduction, replacement, and refinement, as well as regulatory least-burdensome principles with the goal of using the minimum number of animals necessary to generate valid scientific data to demonstrate reasonable safety and performance.

I will first provide some context around this topic with an introduction to the types of marketing submissions that may include animal data and types of data that are provided

in marketing submissions to FDA. I will then discuss a framework for deciding whether animal data are needed in a submission in the context of other data that is being considered for inclusion in the overall data package. We will then get into a few examples of orthopedic device types that typically do and do not include animal data and why. We will recap with conclusions.

The four types of marketing submissions for which animal data may or may not be provided in the data package to FDA include 510(k) or premarket notifications; de novo classification requests; PMA or premarket approval applications; and HDE or humanitarian device exemptions.

Most Class II medical devices are subject to 510(k). De novo classification requests, when granted, provide marketing authorization for a specific device and classify the device type into Class I or Class II. Class III medical devices are subject to PMA. Devices that benefit patients with a disease or condition that affects fewer than 8,000 U.S. patients a year may qualify as a humanitarian use device that may provide a marketing application for an HDE.

For the remainder of my discussion today on animal studies and FDA submissions, this will not be relevant for devices that are exempt from premarket notification or approval, so typically Class I devices and a few Class II. IDE, or investigational device exemptions, for seeking use of a device in a clinical study; EUA, or emergency use authorizations which allow for temporary use of a device that is needed to address a public health emergency; RFD, or requests for a designation for a product type, such as drug, biologic, or device; or 513(g) requests for classification status as Class I, II, or III. Although these submission types can reference animal data, these are not full data packages to support the full marketing of the device in the U.S.

For the purposes of this talk, when we are discussing performance data, we are

referring to three main types: benchtop, animal, or clinical data. Benchtop testing can include mechanical testing, evaluation of device attributes in simulated body fluid or serum from animals, testing the device in in vitro cell culture, testing the device ex vivo in tissues or organs that have been harvested from animals or humans, and cadaver testing.

Animal data, the next category, can include testing the device with living animals, anywhere from small proof of concept studies to comprehensive studies run in large animal models.

Clinical data here refers to data on the safety or effectiveness of the device in humans. This can include data generated inside or outside of the U.S., collected prospectively or retrospectively, anywhere from case series to randomized controlled trials and systematic reviews and meta-analyses.

Data we are not discussing for the sake of today's discussion include simulated studies; biocompatibility endpoint testing, although animal performance testing can be designed to incorporate a subset of the biocompatibility endpoints; sterilization, packaging, and shelf life validation studies; magnetic resonance safety studies or software validation studies.

So now that we have gone through the types of marketing submissions that we are considering animal studies for and have a sense for the other data types that are provided in marketing submissions, it's time to consider how to make the decision of "is animal data needed for my device?"

Five-ten (k)s, de novos, PMAs, and HDEs as marketing pathways do not map directly to whether or not animal data are needed. For each of those file types, there may be cases where animal data was or wasn't included in the decision making.

For Class II devices with established special controls, the first step is to check whether the special controls specify animal data and you may have your answer there. For

device types where the special controls do not specify whether or not animal data are needed, you can consult what data types the predicate device had included for marketing clearance and you can often find this information in the public 510(k) database which will include links to the 510(k) summaries.

If you have a Class II device where you are unsure how to apply the special controls as they relate to animal testing, or if you want to propose alternative methods of meeting the special controls, we strongly recommend that you use the pre-submission process to receive FDA's feedback prior to starting any animal testing.

For Class III devices with a similar device already approved, similarly, you can check what data types formed the basis for approval of that similar device. The PMA database serves as a public record of these approvals and will have links to the public summary of safety and effectiveness data or SSED documents. Again, if you have considerations specific to your device where it is not clear whether you need the same types of data as a similar Class III device, we recommend the pre-submission process.

For novel device types, there may not be an existing Class II or Class III device similar enough to yours that you can apply a similar data plan. For novel devices, these most often fall under the de novo, PMA, or HDE regulatory pathways.

The first step in decision making is to consider whether in vivo data are needed to support performance, meaning anything that is not bench testing. Some questions to lead you to this are bulleted in the slide, though keep in mind that these are not official or binding criteria:

- Are there bench testing methods for assessing the performance claims and potential failure modes which are validated to correlate with clinical performance?
- If preliminary bench testing has already been completed and the results were

anomalous or inferior to those of a comparator, could an in vivo assessment potentially justify that the performance is acceptable for its intended use?

- Is the device implanted in a changing biomechanical or changing biological location over time?
- Are the soft tissues healing?
- Is an infection being treated?
- Is the device an implant with a novel material?
- Does the novel implant material degrade or release any constituents?
- Is the device intended to reduce pain or improve function?
- Is the device intended to function as a scaffold or stimulate, generate, or guide tissue growth or protect other tissue from ongoing disease processes?

For many of these, if the answer is yes, this may be an indication that in vivo data of some kind or kinds may be needed. If in vivo data are needed, the next step would be to evaluate whether animal data, clinical data, or both are needed. Maybe your initial preference is to try to use animal data only instead of clinical data or both. This may be the least resource intensive option.

Some questions to think about are is there an animal that is validated to correlate with the clinical performance for the disease, condition, or treatment over a clinically relevant period of time? If so, clinical data may not be necessary.

In orthopedics, some things to consider are that there are few validated animal models for pain and function outcomes that are predictive of the human experience. Although animal studies can collect preliminary indirect assessments of pain and function such as gait studies, assessments of heart and respiratory rate, observations of appetite, localization, social behavior, and other signs of agitation, these are typically not conclusive on human clinical performance. Additionally, performance endpoints related to

biomechanics over time for devices in the joints and spine are often not adequately represented by quadruped animals if omitting clinical data. Or maybe you already have clinical data or plan to be collecting clinical data and you are trying to see if animal data are really needed for your device.

Some questions to consider are whether tissue imagining, whether on a microscopic histological assessment level or just the gross tissue appearance or if postmortem assessments will be needed. If you don't need either of these, if you can assess everything relevant for safety and effectiveness for your device in the context of your human clinical studies, maybe you don't need animal data for a marketing submission.

Note that even if animal data is not needed in your final marketing submission, once you have the clinical data available, if your device is a significant risk device that you are studying in the U.S. under an investigational device exemption, FDA may require that you provide animal data in your IDE as a preliminary assurance of subject safety in that study.

After you have evaluated whether in vivo data are needed for your device and what types of in vivo data, the next highly suggested step is to start talking to FDA before you start these studies. We recommend that you use the pre-submission program to receive FDA's prior feedback on the test plan. For medical devices, you can submit pre-submissions at nearly any stage of product development and there's no limit to how many pre-submissions you can submit if your plans change, if your device changes, if you have new questions for FDA. In a pre-submission full test protocols are preferred but not required in order to receive feedback. We can also provide a more targeted feedback for your test plan if you break it down to which study or studies will address which device risk or performance goal. For information about the pre-submission program, more information can be found in the guidance document on the Q-submission program.

Now we will jump to a couple examples to show how the framework is applied.

Certain devices, due to the specific indications for use and the existing development of animal models that predict device performance in humans, do not need clinical data in most cases. One of these examples is bone void fillers that are indicated for use in the extremities and/or posterolateral spine.

Stepping through the framework. There is a special controls document for this device type which points out cases where animal data are needed. In addition to the special controls document, there are FDA-recognized standards that describe the validated animal models and how to implement them. The rabbit models are the most common, but FDA has accepted other animal models besides these. You can also look through the public 510(k) database with the product codes associated with this device type and see the performance testing provided for these devices. There are very few cases where clinical data have been used for bone void fillers.

Next, I wanted to share an example of a device type where it may be suitable to use clinical data without animal data to demonstrate performance. Bone indentation devices are devices that measure resistance to indentation in bone. The special controls listed in the classification order refer to in vivo testing but do not specify whether this means animal or human, so there's no requirement for one over the other. However, for this device type, clinical data may be more direct for evaluating the risks listed in the special controls.

Animal models for pain and discomfort due to bone indentation are not currently well developed. Histological evaluation is also not needed to assess performance. Additionally, we are able to define the clinical study endpoints of interest without having any information from animal studies. Currently, this device type would be a good candidate for providing clinical data without animal data.

Finally, there are a few examples I'd like to share of device types with both animal data and clinical data that are generally provided to evaluate performance.

Resorbable implants for ACL repair are classified as Class II and the special controls in the classification order include line items for both clinical and animal performance testing. These devices would be straightforward in the decision making to include both animal and clinical testing in the overall test plan.

Bone void fillers for interbody fusion are a less straightforward case. These devices are generally considered Class II when there are no growth factors or biologic component involved, and considered Class III when there are other growth factors or other biologic components. As with the bone void fillers for extremities and posterolateral spine, animal data are needed to demonstrate bone bridging the dimensions of the filler over time and these are achieved by a combination of histologic and radiographic endpoints of which the histology endpoints cannot be reasonably conducted in a human clinical study.

However, unlike the extremities and posterolateral spine, interbody fusion is currently lacking an animal model that is validated to be predictive of human clinical performance. Until such an animal model is developed and validated, clinical data are likely needed in addition to animal data to allow for assessment of interbody fusion outcomes over a clinically relevant period of time. Product developers can also query the public 510(k) and PMA databases for clearances and approvals of these devices to consider the test plan for their device.

To recap what we've discussed today, animal testing can provide additional information on device performance beyond what can be accomplished in bench testing and address questions of performance in a biologic system beyond biocompatibility testing.

Animal testing can provide a lower variability test system and options for tissue imaging and other postmortem endpoints that are not possible with clinical testing.

Clinical data may be appropriate as the sole in vivo testing or in addition to animal testing. This would depend on how predictive the animal models are for the disease or

condition and also for the device's risks and performance claims.

Regardless of the marketing submission type, a submission may or may not need animal data to evaluate performance.

Whenever possible, you should consider the special controls, any device-specific guidance documents, or past examples of similar devices for information on whether animal and/or clinical data are needed.

And if there's one thing we hope you'll take away from this talk, we strongly recommend that you use the Q-submission program to reach consensus with FDA early on for what is needed for your device prior to initiating animal or clinical studies.

Thank you and we look forward to the discussion.

DR. MOORE: Thank you for sharing this incredibly helpful information with us, Dr. Panigrahi. So thank you to all the Session 2 presenters.

We will now begin our final question and answer session. We welcome our Session 2 presenters, Mr. Kaiser, Dr. Crusan, Dr. Thompson, Dr. Fisher, and Dr. Panigrahi. And they will also be joined by our moderator, Dr. Laura Rose. Dr. Rose is the assistant director in the Division of Restorative, Repair and Trauma Devices in OHT 6 and has been with the Agency since 2016. She has a bachelor's degree in biochemistry from the University of British Columbia, a Ph.D. in biomedical engineering from the University of Alberta, and post-doctoral fellowship completed in radiology at Johns Hopkins University.

To the audience, one last time, please remember you can send in your questions and comments using OHT6-Feedback@fda.hhs.gov.

I'll turn it over to you, Dr. Rose.

DR. ROSE: Thank you, Dr. Moore. I want to thank all of our presenters today for such great presentations and we've had a lot of really good questions come in through the e-mail inbox, as well.

The first question is for Mr. Kaiser. So you've mentioned in your presentation that the guidance process has draft guidances first available that are for comment purposes only and then this guidance is finalized after FDA addresses the comments. In situations where FDA's thinking is evolving but there's not updated final guidances, what should companies do?

MR. KAISER: That's a good question and it's certainly something that comes up fairly frequently, is that you can imagine as we learn more about products, the things that we're taking as our current thinking can evolve over time and the answer to this is the answer that you've heard in quite a few of the other presentations and probably the answer that you'll hear in a lot of the questions that we're answering is "come and talk to us." The pre-submission process is really the way that you can find out how we are viewing a particular question.

And so what we'll end up doing is we'll start with the guidance that we currently have, that's the baseline, that's the existing set of information that we have available, and as we learn more, we kind of fill that out with additional information, potentially alternate information. But really, the way to find out what we're thinking about is to submit a pre-sub, have that conversation with us where we can really tell you what we think.

DR. ROSE: Thank you, Aric. Yes, it does sound like talking to FDA is the first step if you're ever thinking of doing an animal study.

MR. KAISER: First step, the second step, and the third step, keep that conversation going because it really is helpful.

DR. ROSE: Thank you. Dr. Crusan, our next question is for you about GLP studies. Could you please discuss whether CDRH accepts audited draft reports as long as the final report is submitted in a defined time period?

DR. CRUSAN: Yes, thank you. CDRH does not accept promissory notes or submission

of a final report at a later date. CDRH has accepted audited draft reports; however, in our review experience, draft reports lack the complete postmarket analysis for pathological evaluation, which we heavily rely on for safety review and decision. So this will not be acceptable if the pathological report is incomplete. We also have less confidence in draft reports as these can be further amended. Depending on the draft report and where you are in the submission process and what other data you have, we recommend that you come back in to talk to us through the pre-submission process.

DR. ROSE: Thank you, Dr. Crusan.

Dr. Thompson, next question is for you. For the evaluation time points that you mentioned in your presentation, is there a recommended percent of degradation that should be achieved by the late, the final time point or is it simply enough to show that the degradation is occurring?

DR. THOMPSON: Very good question. The degradation time points, there's not sort of -- or the time points based on degradation, there's no really set in stone, you know, a one-size-fits-all approach to that. There's a lot of variability in the degradation rates that these devices have and really, the objective is to look at the trends and to see where the rate is headed. We tend to want to see at least a steady state reached. You know, if there is a lot of material left at the final time point, we might ask for an additional time point so we can see a little bit more progression because the more material, there's more potential for a biological response happening.

I think that it is really important to do pilot studies or bench testing, just get as much preliminary data before embarking on the animal study because we can use that data to inform decisions about what the time points are so that before the study is initiated there's kind of a general idea of what's going to happen and then there's no surprises when that, you know, at 6 months there's still a bunch of material and we don't have animals to keep

going further out and too, you don't have animals at a year when they really didn't need to be continued out that long, so we save animal numbers in both ways. Again, I think this is going to be a theme throughout the day, discussing it with us is the best way to determine what the time points should be. Sometimes we don't look at like full data reports during the Q-sub process in general, but we can certainly do some preliminary -- you know, look at some summaries and things of the bench testing and some of that preliminary work to help guide you in your choice of time points in the study.

DR. ROSE: Thank you, Dr. Thompson.

The next question is also for you, Dr. Thompson. You mentioned in your presentation that rabbits are generally preferred over mice and rats for the animal performance implantation studies, but there are some devices that might contain things like human tissue and there might be an adverse tissue response when these human-containing tissues are implanted into a rabbit and that same response would be seen in a human patient.

One of the questions in the chat is asking about implantations to athymic rats and whether that would be an appropriate model to adjust some of the cellular and humeral responses. Could you please comment for us on testing devices that contain human tissue in athymic rats to better study the local response?

DR. THOMPSON: Sure, yeah. This is certainly a question that does come up in the course of these reviews. I think the important thing to remember when we're looking at this species and the model is that regardless of the device or the animal for these functional studies, we're looking at performance. And so with a bone product, it's difficult to assess these, evaluate these in a rodent model, like a rat, because of the differences in the bone physiology. One thing that can sometimes be done with these human tissues is you could consider creating an animal version of the product. An example would be with the

demineralized bone matrix, those types of bone void fillers, if you are using a rabbit model sometimes you might be able to create the product with the bone void filler using a rabbit tissue and the thing that we would want to emphasize in this particular example would be that that product, regardless of whether it's animal tissue or human tissue would need to be processed in the exact same way because we want to look at that final finished device and if it's not processed in the same way, then there would be questions about how that would perform.

And sometimes, too, if there are questions that really can't be answered with the animal model, sometimes we look at clinical evaluations, as well. So if it truly is a challenge and the data is not generating very useful information, then we may ask for some clinical data just to give us some assurances of safety and performance. Again, that would be a really great question to bring up to us to discuss before embarking on any of these animal tests because there's a lot of nuances to it and it could be very sort of device specific and so that would be a really good conversation to have with us.

DR. ROSE: Thanks, Dr. Thompson. I think that's one of the key messages that we're trying to get across here is that there is a lot of nuance with these animal studies and having the chance to talk with us and for us to provide feedback for you, that's really what we're hoping to get out of those interactions is be able to discuss some of those nuances in the animal studies.

Dr. Crusan, the next question is for you. So we've heard some insightful information of differences in anatomy and skeletal maturity between animals, so for instance, between sheep and canine, it seems that scientists have generally used only one sex, generally male, for animal experiments and have applied findings to both sexes. What considerations are there for male versus female animals when selecting and reviewing representative animal models for studies? How is the sex of the animal considered as a biologic variable in terms

of evaluating animal studies and worst-case contracts for orthopedic applications?

DR. CRUSAN: It is absolutely right that sex of the animal is a variable. In biocompatibility studies we ask to keep performance studies in both sexes, male and female. However, with regards to large animal studies, consideration including both sexes should balance with a minimum use of the animals which would give meaningful safety data, which means in many large animal studies we see, for orthopedic devices, we see only one sex of animals to minimize confounding effect of the sex if there is any.

We also consider what the species is, the handling and housing of the animal. We only ask that if using female large animals that they are not lactating or pregnant since this will impact the review of the performance and safety of the device. We definitely take into consideration during the review what the sex of the animal model is and we'll recommend use of both sexes depending on the device, the data, and the literature available or patient data we have reviewed about similar devices.

DR. ROSE: Thank you, Dr. Crusan.

The next question is for Dr. Thompson. Could you please discuss about animal models for study of intervertebral discs and intervertebral fusion?

DR. THOMPSON: Sure, that's a great question because I feel like this, in particular, is one of the more challenging models to work with, particularly because it's difficult to create the pathology that's required to evaluate these types of devices. And I think the best models are going to be really based on the device type and also on the objective of the study, so I think this is a really important place to talk with us and discuss these types of things early on. Some of the considerations would be the site of implantation, so the lumbar spine versus the cervical spine. When we're looking at these types of animal models we want to mirror the clinical application as closely as possible. So if a device is intended for the lumbar spine, then I definitely would recommend using that in the animal model.

I thought that Dr. Cook's presentation was really interesting on this front because he mentioned the dachshunds and other animals that suffer from intervertebral disc disease being potentially really useful subjects to inform our device development for the human and I think that to me, that seems like an untapped resource because you have naturally created pathology that is very similar to the human pathology, albeit in a quadruped versus a biped, but that is something that really impacts these dogs' lives and the humans that own the dogs and so I think that there would be a lot of people willing to sort of jump in and use a clinical veterinary trial to work on getting these, sort of fine-tuning these devices and making them better.

DR. ROSE: Thanks, Dr. Thompson. Yeah, I love that you mentioned the ability to potentially get information from the veterinary patients, as well, and I especially liked some of the morning talks that talked also about being able to apply what the veterinarians have learned from the studies onto our companion animals. Could you talk to us a little bit more about what somebody should do if they're interested in using that type of study or data to support a marketing application?

DR. THOMPSON: As far as like submitting veterinary clinical data to us at the FDA? Yes, I think that (1) that would be a really great Q-sub topic for the Q-submission process because then we can look at that data and see what it can help, sort of the questions that it can answer if there are remaining questions and we can look at okay, do we need to have some safety studies to supplement this, you know, is this going to guide a clinical trial. We've certainly had submissions that have included veterinary clinical data and I think those are really interesting ways of capturing some of these, you know, some information about these devices. So I would say certainly to start early in the process with giving us that information and make sure that if you're going to do a veterinary clinical trial, even before you start the trial, come talk to us because we would be happy to do that even though it

seems like well, it's veterinary, it's not human, but if it's going to inform a human device, then I think that we would love to be involved in that process early on.

DR. ROSE: Thank you. Yes, it does seem like it's an area for synergy in the future, is where you can benefit both human patients and veterinary patients, as well. Thank you.

Next question is for Dr. Fisher. Could you please describe whether it's possible to use software to do the histomorphometric analyses that you discussed in your submission? Or your presentation?

DR. FISHER: Yes. An automated method for process may be used to perform the histomorphometry analysis. We would ask that you please ensure that this method can distinguish between new bone, host bone, any fibrous tissue, residual implant that's present, any void space. And then ensuring, also, that the method that is being used to perform the analysis was validated for the implant.

DR. ROSE: Thank you, Dr. Fisher.

Mr. Kaiser, we have a question for you about being able to leverage different types of studies. One question that's come up has been abut animal studies to support dental -- or dental studies to support orthopedic indications and I'll ask about the reverse, as well. Could you talk to us about the ability to leverage animal data from other indications, so for instance, from dental, to support an orthopedic use?

MR. KAISER: Sure, I mean the key here is that the data that you've generated and you're trying to use to support the characterization of your product actually matches up with how that product is intended to be used, so is the model clinically relevant, and in this case, data from a dental animal model wouldn't necessarily be relevant to an orthopedic animal model and therefore wouldn't match up with the human clinical use. And one of the things that we've heard people tell us in the past is that you've got bone in the mandible, you've got bone in other places that are orthopedic locations and bone is bone and

therefore we can use data from a dental model to address orthopedic issues. And while it's true that there's certainly bone in the dental space, it's in a totally different environment and so the response of that bone wouldn't match up with the response that you would expect to see for orthopedic uses and because of that, we really want the models to match.

And so an orthopedic fracture clinical scenario, you couldn't extrapolate dental tooth extraction socket data, they're both bone, you're filling a hole in both cases, but they're two totally different uses, different loading environments, different biological environments, and they respond to be very different, so the answer is really match the model to the clinical scenario, the animal model with the clinical scenario and stick with ortho.

DR. ROSE: Thank you, Aric, for that explanation. I think this is a particularly important topic and it probably emphasizes why it's important to come talk with us before starting your submissions or your animal studies.

MR. KAISER: Right.

DR. ROSE: If you think -- you know, you might have plans for one type of study to support another type and we may or may not agree with that assessment, so it sounds like that's another --

(Cross-talk.)

MR. KAISER: It's back to the pre-sub as the answer. Really, we understand the amount of time and the amount of money and the amount of effort that it takes to run an animal study and we really want to make sure you're doing the right study and so talk to us first, get our input on the selection of the model, on the design details, and that when you actually go and do the study you're doing the right study and you're really not wasting a lot of time and money and animals.

DR. ROSE: Um-hum. Thank you, Mr. Kaiser.

Dr. Crusan, the next question is for you. Could you talk a little bit about the quality

assurance unit and how it would assess the validity of imaging data that's used in orthopedic studies? How would any lack of validation be reported as a GLP exception in the final study report? Could you tell us a little bit more about that, please?

DR. CRUSAN: Yes. To answer this question, we refer you to the regulations, 21 C.F.R. Part 11 on electronic data and signatures. The regulations in this part set forth the criteria under which the Agency considers electronic records, electronic signatures and handwritten signatures executed to electronic records to be trustworthy, reliable, and generally equivalent to paper records and handwritten signatures executed on paper.

So in a way, we just wanted to make sure that the QAU was able to verify that the imaging SOPs, including the documentation and recording are followed and that the images can be tracked to the individual animal and to a certain time point. So I think that we generally do not look at how the imaging data or how the imager is validated, but we do want you to make sure that the diagnostic imager or that the machine is calibrated and maintained in a timely manner.

DR. ROSE: Thank you, Dr. Crusan.

Dr. Fisher, next question is for you. So we've heard throughout these presentations that one of the things that we are recommending is a negative control which consists of an MT defect and for the discussion of the bone defects, the number that we've heard was 10% and that was to make sure that we have this critical-sized defect that doesn't heal spontaneously. Could you please talk a little bit more about the rationale behind the 10% and whether we need to have that critical-sized defect and maybe why we are looking for that critical-sized defect?

DR. FISHER: Yeah, sure. So the emphasis is placed on the use of a critical-sized defect because it serves to validate that the study was conducted appropriately, so it allows us to evaluate the results for a baseline response and it can help to show how the device or

any devices that are included in the study may have impacted the results. We would recommend the use of a literature validated critical-sized defect model for the selected species and if there's uncertainty about the size or animal model, specifically, then a pilot study could potentially be used.

Regarding the potential healing, the 10%, especially like in a young animal, we recommend ensuring that the animal is skeletally mature. This not only ensures the proper size of the animal, but it also -- if the animal is younger and it's not skeletally mature, then more bone growth than anticipated might occur. As an addition to that, we would also recommend focusing on the execution to make sure that the technique is appropriate.

DR. ROSE: Thank you, Dr. Fisher. So if I understand what you're saying, what we're really looking for in that negative control, in that 10%, is to be able to show a clear difference between what would happen if nothing was implanted into that defect versus ideally seeing some sort of positive response from the device. And so it essentially ensures us that your device is doing something and we're able to measure that performance and have some sort of comparison to the positive control which, as you and others have mentioned in the presentation, is probably going to be autograft or some sort of standard of care or another legally marketed device, is that right?

DR. FISHER: Correct, yeah. And it helps to validate those results and it provides us with -- it allows us to know that the results are reliable.

DR. ROSE: Thank you. I think my next question for -- my next question is going to be for Dr. Panigrahi, a little bit more about some of the animal data and its role in premarket submissions. Can you maybe suggest to us some additional thoughts on when animal data would maybe be considered adequate by itself versus animal and clinical or even clinical, do you have any other thoughts on that?

DR. PANIGRAHI: Sure. Thanks, Laura, for the question. So that will really, really

depend on the device itself and the intended use, right? So it's going to depend on how established these are and what we really need to evaluate, the safety and effectiveness. It will also depend on what the existing standard of care treatment is and how that is best evaluated. It's going to depend on the endpoints that are relevant to establishing safety and effectiveness.

For a device where the intended use, the main intended use is to reduce pain or improve function, it might achieve those by reaching some additional functional endpoints. But if the primary way of measuring effectiveness is going to be evaluating the pain, evaluating the function, most likely, for orthopedic devices, clinical data are ultimately going to be needed.

Animal data can provide additional explanation about what is going on in the tissue. It can help provide initial correlative information between, for example, CT and histology and gross pathology findings that you wouldn't necessarily get from the clinical data.

So it will really always come down to what are the specific risks of the device type, what are the performance goals of the device, and that will be in part defined by the product developer themselves, like what is the device intended to do. And then it will be affected by how good are the existing animal models for showing that a device does or doesn't meet the performance goals, showing that the device does or doesn't address issues related to safety for that device type, for that intended use population. So unfortunately, my answer to this is it depends and I will echo everyone else in the room in that it is really helpful to come talk to FDA about your specific device, you know, technology is constantly changing, we are constantly on the lookout for new innovations, to address known and developing patient conditions and our technology is always going to be developing, so the endpoints needed to evaluate that technology are also going to be developing over time. Thanks, Laura.

DR. ROSE: Thank you, Dr. Panigrahi.

Dr. Thompson, would you like to make one final comment?

DR. THOMPSON: Yes, I just wanted to emphasize that one of the big goals today is to really make sure that these studies are really well done and that they're well done the first time. And it is our goal at FDA to really save as many animals as we can, we don't want to have animals used needlessly, and myself and the other veterinarians that are looking at these animal studies when we're reviewing these files, we are so mindful of that and really want to work towards using methods that minimize animals, using alternative methods, because it's just so important to us as vets, we love animals and we all have animals, and I sit at my desk and I -- you know, we work from home, I look out over my fields and I have little sheep and sometimes it's hard for us to look at these studies and see the animals that are used for them.

But I also always remind myself it is so important, our job is so important as stewards of public health, and if these animals don't die in vain, that information is so important and we use it and we talk about it and we debate it and it's something that really helps make the clinical studies and the clinical use of these devices so much safer and make sure that they work and do what they're supposed to do and without these animal studies, I just think that we would not have that, you wouldn't have these safety measures and it wouldn't be -- you know, you wouldn't have as many devices, probably, even on the market because it would be harder to do that. And some of these devices are really lifesaving devices, I mean, some of them are not even a life or death device but even a device that manages pain, I mean, that is such a big problem in our society. And so I just wanted to emphasize that because I know there can be controversy surrounding animal studies and animal research and I just want everybody to realize how important it is to us at the FDA for that.

DR. ROSE: Um-hum. Thank you, Dr. Thompson.

With that, I'd like to thank all of the speakers in Session 2 for your presentations and for your insightful comments in the panel discussion here. I'm going to turn things over back to Dr. Moore. Thank you.

DR. MOORE: Thank you, Dr. Rose. I just want to say thank you one more time to all of you that are virtually participating and thanks for sending in some great questions.

So it has been my pleasure to serve as Mistress of Ceremony for today's workshop. On behalf of FDA, I would like to thank all of the speakers for the great presentations and very informative dialogue. To all of you in the audience, thank you for staying engaged and contributing some excellent questions.

I will now ask Dr. Laurence Coyne to provide the closing remarks. Dr. Coyne serves as the division director of the Division of Restorative, Repair and Trauma Devices, also known as DHT 6 C in the Office of Orthopedic Devices or OHT-6. Prior to his current position, Dr. Coyne's 30-year career in FDA has also included serving as an assistant director in OHT 6; a branch chief in the Office of Device Evaluation; a first-line supervisor and director of the engineering branch at the Winchester Engineering and Analytical Center, known as WEAC; an FDA field laboratory; and a materials research engineer in CDRH's Office of Science Technology, now known as the Office of Science and Engineering Laboratories. Dr. Coyne has a doctoral degree in polymer science and engineering from the University of Massachusetts at Amherst and a bachelor degree in clinical engineering from Tufts University.

Take it away, Dr. Coyne.

DR. COYNE: Thank you very much, Dr. Moore.

I'm Dr. Larry Coyne, a division director within the Office of Orthopedic Devices in FDA's Center for Devices and Radiological Health. I have the distinct privilege of providing

closing remarks for what has ultimately been a very informative and successful workshop. We can all readily agree that today's workshop has fully succeeded in sharing a plethora of valuable information and best practices regarding animal studies intended to support premarket submissions for orthopedic products. I also wish to reiterate FDA's support for the principles of the 3Rs, to reduce, refine, and replace animal use in testing when feasible. We encourage sponsors to consult with us if they wish to use a non-animal testing method they believe is suitable, adequate, validated, and feasible, and we will consider if such an alternative method could be assessed for equivalency to an animal test method.

In summarizing today's workshop, Session 1 began with presentations on comparative anatomy and practical considerations for choosing an appropriate animal model for an orthopedic study. These were followed by presentations on best practices for orthopedic specific animal models intended to assess bone graft products for use in the extremities, cartilage repair products, spinal fusion devices, and non-fusion spinal devices including intervertebral disc replacement devices and pediatric use devices including spinal growing rods and chest cage expansion devices. Next were presentations on considerations for assessments and study endpoints for orthopedic animal studies and a discussion of opportunities for a clinical translation of veterinary clinical trials.

Session 2 of the workshop included presentations on voluntary consensus standards in FDA guidance applicable to animal models and animal studies; a detailed look at elements of good laboratory practice; regulations for animal studies; best practices for choosing an animal model and design considerations for premarket animal studies; elements to include in study protocols and test reports for animal studies; and regulatory considerations for assessing the need for animal performance data in various types of marketing submissions.

Both Sessions 1 and 2 were followed by enlightening question and answer

discussions which served to further elaborate upon and to provide an even deeper understanding of the content of all of these outstanding presentations. All in all, this has been a tremendously successful workshop.

In closing today's workshop, I would like to express our gratitude to all those contributing to the success which included all of today's speakers; our Mistress of Ceremony, Dr. Kira Moore; our session moderators, Dr. Sara Thompson and Dr. Laura Rose; Captain Raquel Peat and the Office of Health Technology 6 leadership; FDA's Office of Communication and Education; and FDA Studios for enabling this event to happen; Dr. Liza Fisher; Mr. Aric Kaiser; Dr. Pooja Panigrahi; Dr. Thompson and Dr. Rose again; Lieutenant Commander Randoshia Miller and everyone else in FDA who took part in planning and organizing this event. Lastly, I would like to thank every one of you in the audience for your participation in this workshop and to wish you all a very good remainder of the afternoon.

This concludes today's workshop.

(Whereupon, at 12:55 p.m., the meeting was adjourned.)

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C E R T I F I C A T E

This is to certify that the attached proceedings in the matter of:

VIRTUAL PUBLIC WORKSHOP – ANIMAL STUDIES FOR ORTHOPEDIC PRODUCTS

June 2, 2022

Via Microsoft Teams Videoconference

were held as herein appears, and that this is the original transcription thereof for the files of the Food and Drug Administration, Center for Devices and Radiological Health, Medical Devices Advisory Committee.

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