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CENTER FOR VETERINARY MEDICINE PUBLIC WEBINAR: GENOME EDITING IN ANIMALS

I. Welcoming Remarks and Goal: Dr. Steven Solomon, Director, Center for Veterinary Medicine (CVM) (slides 1-3)

Hello everyone. We're very pleased you could join us today for FDA's public webinar about genome editing in animals. I'm Steve Solomon, Director of FDA's Center for Veterinary Medicine or CVM, as you'll hear folks say throughout the presentation today. In addition to staff from CVM, we're also fortunate to be joined by our colleagues from FDA's Center for Biologic Evaluation and Research or CBER. I'd like to welcome them as well and thank them for their collaboration in today's webinar. I also want to thank them for our ongoing shared efforts to scientifically review products of emerging technologies like genome editing.

Last fall, the Commissioner's Office released FDA's Plant and Animal Biotechnology Innovation Action Plan. This webinar is one of the action items announced as part of that plan. Before we move any further, I want to emphasize that today's webinar will focus on intentional genomic alterations in animals. You may hear us say IGA as shorthand. We will not cover genome editing in plants including plants used for human or animal food. Here at CVM, our mission is protecting human and animal health. Meeting this mission is what motivates the staff at CVM, who are deeply committed to public health and passionate about animal health.

We're part of the overall federal government effort to protect public health and the environment. We do this by adopting regulatory approaches that are proportional to identified risks posed by the products we regulate. One of the ways of accomplishing our mission is by encouraging the development of innovative products such as intentionally genomically altered animals that have significant potential to enhance public health. We're also making sure these products are safe and perform as expected. This is critical to maintaining consumer, patient, and commercial confidence in these products. We're committed to making regulatory decisions based on sound scientific and technical evidence. We're also committed to making regulatory determinations based on the characteristics of a product and its intended end use. You'll hear more about this continuum later in the webinar. Specifically, CVM is committed to using an appropriate risk-based regulatory framework. We're basing this framework on sounds science to further advance emerging technologies to develop safe and effective products, while ensuring consumer confidence. We want to make sure our approach is tailored to the opportunities these technologies enable. We're also cognizant of the unique ways in which many genome-altered animals are and are going to be raised including on farms.

We're excited that genome editing provides great promise for the development of animal biotechnology products that benefit human and animal health, improve animal well-being, and enhance food production and safety. We also understand that unique hazards associated with the use of genome editing should be properly evaluated, especially when the alterations are in food-producing animals. This ensures safety to animals, humans and the environment. The science is rapidly evolving, and new more specific technology is

becoming available that may mitigate potential hazards which underscored the need for a flexible risk-based approach. We at CVM and FDA have the scientific expertise needed to appropriately evaluate products of animal biotechnology. As previously mentioned, we also have the mission and credentials as a public health regulatory agency. Our oversight fosters development of emerging technology products of public health significance while enhancing consumer confidence in the safety of these products.

Here in CVM, we have a newly formed Division of Animal Bioengineering and Cellular Therapies or ABCT Division. This team has assembled the critical expertise across a wide array of scientific disciplines. The team will be able to evaluate this science and provide risk based regulatory oversight ensuring safety and efficacy. Its members include molecular and cellular biologist, bioinformaticians, geneticists and genomics experts, chemists, stem cell biologists, animal scientist, and veterinarians. The team has expanded to meet the scientific expertise needed to assess new products under development and to enhance the efficacy of the review process. But this team is not working in a vacuum. Fostering innovation is a collaborative effort across the agency. In particular, CVM meets regularly with our colleagues in CBER. We discuss recent scientific advances associated with genome editing in animals and humans including biopharmaceuticals under development. Later in the webinar, colleagues from CBER will provide information about genome-editing products for xenotransplantation in humans. They'll also talk about how we work together across the agency to regulate these problems. So now let me turn it over to Dr. Heather Lombardi. Dr. Lombardi will go over the agenda, and, once again, thank you all for joining us today.

II. Agenda: Dr. Heather Lombardi, Office of New Animal Drug Evaluation (ONADE), CVM (slide 4)

Thank you, Dr. Solomon. Hi, my name is Heather Lombardi, and I'm a team leader in the Division of Animal Bioengineering and Cellular Therapies in the Office of New Animal Drug Evaluation at the Center for Veterinary Medicine. Thank you for joining us today for our public webinar to discuss genome editing in animals. Our agenda today will cover an overview of genome editing in animals, use of products incorporating genome editing for the treatment of humans, our risk-based regulatory approach for animal biotechnology, and a session about clearing up the confusion addressing common questions about FDA regulation of animal biotechnology. And lastly, we'll conclude with a question-and-answer session. This webinar is primarily geared toward sponsors or developers that are working with genomic alternations in animals produced using genome editing, although it's open to everyone. In the future, we plan to hold other public conversations addressing other types of stakeholders. This webinar is not meant to address comments received in response to the publication of draft Guidance for Industry 187, "Regulation of Intentionally Altered Genomic DNA in Animals," nor is it meant to discuss proposed revisions to the guidance. We are working to finalize the guidance and will communicate the details at a future date.

The speakers presenting today consist of experts from across the agency, including a member of CVM's Division of Animal Bioengineering and Cellular Therapies, the Office of the Director, the Office of Surveillance and Compliance, as well as CBER's Office of Tissues and Advanced Therapies. The webinar will be recorded and will be posted for future reference following its conclusion. Thank you again for joining us, and we look forward to working closely together with you to bring products using this promising technology to market. Now I will turn it over to my colleague Stella Lee.

III. Overview of Genome Editing: Dr. Stella Lee, ONADE, CVM (slides 5-14)

Thanks, Heather. Hi, my name is Stella Lee. I am a biologist reviewer from the Division of Animal Bioengineering and Cellular Therapies, and my background is in human genetics and molecular biology. I'm very excited to be here with you to give you an overview of genome editing in animals. So first of all, what is genome editing? In brief, it's a technique utilized to make specific changes or edits to the genome. DNA can be inserted, deleted, or replaced at a specific location in the genome using site-specific nucleases, which you can think of as scissors that are designed to cut the DNA at specific target sites in the genome.

Next, I'd like to introduce the three most commonly used genome-editing tools which share two common features. First, it has a nuclease component, scissors that can cut the DNA, and then the second component is that they're designed to locate and bind to the target sites through DNA binding of proteins or RNA. The first two tools use DNA binding proteins. The first one is called zinc finger nucleases, which use the zinc finger transcriptional factor fused to a fok 1 endonuclease. The second one is called TALENs, transcription activator-like effector, that are, again, fused to Fok1 endonucleases, and these two require two arms to come together to the DNA to dimerize the Fok1 and result in the double-strand DNA break. Finally, the most commonly recently used genome-editing tool, called CRISPR-Cas system, uses a combination of a protein, Cas9, as shown here, which is the nuclease component, and a short RNA, shown here as a guide RNA that will guide and lead the Cas9 to the specific target site in the genome, and because it uses RNA, it's relatively easier to manipulate. Research is ongoing to further develop and improve these genome-editing tools to enhance their efficiency and specificity.

So, how does genome editing work? Let me walk you through a simplified diagram. A site-specific nuclease that was described in the previous slide will bind to a specific target site in the genome. Then it will make a double-stranded DNA break. Double-strand DNA breaks are toxic to cells, so cells have their intrinsic mechanism to signal a DNA damage response, and so this break will be repaired by using cells' endogenous repair machinery. In other words, the same DNA-repair pathway that regularly repairs double-strand DNA breaks would also be the main players that are involved in the genome-editing process. There are two main DNA repair pathways. Non-homologous end joining is the most common pathway, and it's active throughout the cell cycle. It's considered a quick way to glue back two broken ends of DNA; as an outcome, it may lead to random small insertions or deletions. This pathway is known to be error-prone, which is preferred if the intended outcome is to disrupt the gene sequence. On the other hand, homology directed repair is considered to be precise pathway. It is important to note that this pathway is only active in a certain time of the cell cycle and requires a template sequence. Using its sister chromatid as a template sequence, it can repair the break and restore the original sequence. However, if exogenous template sequence is provided that contains the intended alteration, then they would use that template sequence and the resulting genome sequence will now contain that desired edit. This can be adding a new transgene or specific insertions or deletions at that target site or can be small-scale changes such as a single base pair substitution. The key aspect of genome editing is to make sure that double-strand break potentially occurs only at the target site. And the rest of the process is relying on the cell's own repair machinery, hoping the break was repaired or edited through NHEJ or HDR, resulting in the intended alteration in the genome.

Now one can edit the genome much easily and faster using these innovative tools. Advantages of genome editing include that they are more efficient and take much less time to make such specific changes to the genome when compared to traditional approaches. In particular, CRISPR/Cas systems are relatively easy to use. For instance, there are online

tools to design guide RNA sequences and it's relatively easy to execute the experiment. As mentioned before, the specificity and efficiency of the genome editing tools are continuously improving. For instance, developing and identifying new and better Cas proteins and excitement of the potential of using genome editing has grown tremendously.

Next, I'd like to discuss the promising uses of genome editing and animals. Please note the following examples are part of a broad spectrum of applications where genome editing can be used in animals. First, genome editing in animals can be applied towards human health improvements, such as making edits in animals to reduce transmissions of certain infectious diseases to humans. Also, genome editing can be used to produce products intended for human therapeutic uses: animals to produce human drugs and biologics (known as “biopharm animals”). In addition, the shortage of human organs for transplantation can be potentially alleviated by using genetically altered animals. The genetic alterations in such animals can prevent rejection by the human immune system. Our CBER colleagues are going to talk more about this in our webinar. Animal models of diseases are currently being developed using genome editing and this will allow researchers to better mimic the disease pathways and test potential therapeutics in a preclinical setting.

In addition, genome editing in animals can also improve animal health and husbandry practices. Producing animals to be resistant to deadly and costly animal diseases would greatly benefit agricultural livestock. In addition, tolerating drought or heat can potentially address challenges related to those issues in animal husbandry. Some studies indicate that feeding the increasing global population in the future will require a significant amount of increase in food production, and genome editing can be used to enhance food production, food quality traits in animals; for instance, to have better nutritional benefits, faster growth to market, improved feed efficiency, et cetera.

While there's a great excitement related to the use of genome editing, there's also unique considerations associated with the use of genome editing. First, there can be off-target effects, which can be caused by nucleases possibly making double-strand breaks at other sites in the genome. These can be small- to large-scale alterations. The degree of reported off-target effects varies depending on studies, which actually highlights the importance of the experimental design; for instance, the guide RNA sequence in terms of the CRISPR/Cas system. It's been shown the site-specific nuclease specificity and fidelity depends on multiple factors including the chromatic structure, the cell culture condition, the cell types, dosing, etc. In addition to off-target effects, there could be unintended undesired on-target alterations, and I'll show some examples in the next slide. There's also a potential for unintended biological consequences, such as animal safety issues caused by off targets or even on-target alterations affecting other biological pathways that one cannot predict. Finally, there could be unknown long-term effects with alterations that were made in germline cells that aren’t apparent in the early generations.

Here I'd like to go over the examples of unintended on-target alterations due to double-strand DNA breaks. See the target break site is shown in yellow and the intended alteration is shown in green. Recent studies identified that there are deletions at the target sites including small to large scale. Some deletions were large enough to even affect the neighboring genes. They also saw insertions of different sequences at the target site as well as inversions. There are lesions including inversions up and down stream of the target site as well as chromosomal translocations. These studies that saw these large-scale deletions and chromosomal rearrangements emphasize that these could be possibly missed depending on which sequencing analysis method was used. While these unintended on-target alterations and off-target effects may not always occur, it's important to consider

these potential possibilities when using genome editing because the size or location of such genomic alterations does not directly correlate to its impact. While single nucleotide changes, called point mutations, may not result in any serious consequences, there are many examples of human and animal diseases associated with a single nucleotide change (a point mutation), such as cystic fibrosis, sickle cell anemia, glycogen storage diseases, etc. Also, it's well-known that a mutation in a coding region can impact the protein expression but it is also known that mutations in the non-coding region can impact the gene regulation or gene expression not only in the proximate location but also the distal location in the genome. And mutations in these non-coding regions have been shown in many different types of cancers as well as genetic disorders.

It's important to identify any unintended on- and off-target alterations. However, there are some challenges to address such effects. First, there's no standard detection method in the field to identify off targets. Also, there is genomic variation in each individual that should be accounted for when analyzing sequencing data. Here are categories of a subset of off-target detection methods and each has its own advantages and disadvantages. Researchers should choose the most appropriate comprehensive and orthogonal method based on their experimental design. The first category includes *in-silico* assays, which use computational algorithms to predict the likely off-target break sites. And then they would do further analysis such as targeted sequencing looking at the sites to see if there's actual mutations. The biggest limitation with these *in-silico* assays is that each platform varies based on the different algorithms and the results may be different. There could be intrinsic bias because the algorithm is based on how the researcher thinks the nucleus works based on, for instance, the sequence of the guide RNA or TALENs. Generally, it's recommended not to solely rely on these *in-silico* assays but also include additional methods such from the following categories.

The next two categories look for actual break sites at the genome-wide level, but they differ based on whether this was done in an *in vitro* setting (biochemical assay) or done within cells (cellular method). CIRCLE-Seq, SITE-Seq, DiGenome Seq are examples of *in vitro* biochemical methods. Briefly, they purify the nuclease and allow it to cut the cell-free genomic DNA, then do the sequencing to detect the double-stranded breaks. These are relatively sensitive, and they can detect low-frequency off targets. However, the results may vary from those *in vivo* situations and they cannot fully predict the break sites or alterations that occur inside cells. On the other hand, there are several methods that capture the double-stranded DNA breaks that occurred endogenously within cells, such as guide-Seq, BLISS, BLESS, etc. These assays detect the break sites within the cells, but the sensitivity of these assays may vary based on the cell type and rely on certain factors such as the transfection efficiency or NHEJ etc. The transfection efficiency is low in certain cell types, such as the primary cells, so the sensitivity may be low in those situations. While whole genome sequencing can be part of these previous methods, it can be used by itself to detect off targets and edited animals. The sensitivity of whole genome sequencing highly depends on the sequencing coverage and it can be low in heterogeneous cell populations. When used with proper controls, it can be helpful for analyzing single cell clones or non-mosaic F1 animals. Again, currently there's no gold standard for off-target detection methods. And please note only a subset of available methods were mentioned here. I want to emphasize there's a great effort in the field to standardize the off-target detection methods. In the meanwhile, researchers are recommended to choose the most appropriate comprehensive method that depends on their experimental design.

Finally, I would also like to highlight that not all unintended edits would necessarily lead to an adverse event. In other words, there could be off-target mutations that are synonymous or non-deleterious. Further, phenotypic analysis including animal health data

or nutritional composition may be necessary to fully predict such effects. That being said, better understanding of any potential unintended alterations can prevent or alleviate adverse events. With that I would like to turn it over to my colleague from CBER, Anna Kwilas, who will talk about the use of products incorporating genome editing for the treatment of humans.

VIII. Genome Editing for the Treatment of Humans: Dr. Anna Kwilas, CBER (slide 15-21)

Thank you, Dr. Lee, and thank you to everyone at CVM for having us here today to talk to you. My name is Anna Kwilas and I'm a chemistry, manufacturing, and controls reviewer in the Center for Biologics Evaluation and Research Office of Tissues and Advanced Therapies (OTAT). In CBER OTAT, we regulate human gene therapy products including those that incorporate human genome editing. Human gene therapy products mediate their effects by transcription or translation of transferred genetic material or by specifically altering host genetic sequences. OTAT therefore regulates products that utilize human genome editing when the target of the editing is the human genome. CBER has been regulating human gene therapies incorporating genome editing for over 10 years, so we have extensive experience with the regulation of these types of products. Currently in-house we have 24 products at the IND stage, 27 at the pre-IND stage, and 13 at the pre-pre-or INTERACT stage. Multiple different types of genome editing technology have been used in these products, including zinc finger nucleases, TALENs, and CRISPR, as were discussed by Dr. Lee, as well as other cutting-edge genome editing platforms. These products include directly administered products as well as genome edited, *ex vivo* modified cells that are used to treat multiple diseases, including HIV, sickle cell disease, and cancer. However, please note these products do not include human germline genome editing.

In addition to reviewing gene therapies, OTAT also reviews xenotransplantation products, including cells and tissues derived from genome-edited animals that are used to treat human diseases. Xenotransplantation includes any procedure that involves the transplantation, implantation, or infusion into a human recipient of either live cells, tissues, organs from a non-human animal source, or human body fluids, cells, tissues, or organs that have had *ex vivo* contact with live nonhuman animal cells, tissues or organs. Examples of xenotransplantation products derived from genome animals may include skin, kidneys, or pancreatic islets. Gene therapies incorporating genome editing as well as xenotransplantation products are regulated by OTAT using a science-based approach with consideration to the benefits and risks of each product for each intended indication as Dr. Lee discussed. Genome editing has the potential to correct or remove defective or interfering genes. However, this comes with the risk of off-target genome modification and other unintended consequences, as described by Dr. Lee, as well as the potential unknown long-term effects of on- or off-target genome editing. In OTAT, these risks are assessed in very similar ways to those discussed by Dr. Lee. Dr. Heather Lombardi will further discuss risk analyses as they pertain to genome-edited animals later in this webinar. Unfortunately, at this moment, my colleague Judy Arcidiacono is not here yet. She'll be arriving very shortly, so I'll hand it over to Heather Lombardi to present and then we'll come back to Judy's presentation on xenotranspantation. Thank you.

IX. Risk-based regulatory approach: Dr. Heather Lombardi (slides 22-36)

We're going to skip ahead to my portion. Hello again. In my portion of the presentation I am going to discuss the regulatory process for intentional genomic alterations to the germline of animals related to products produced using genome editing. At CVM we utilize a flexible risk-based and science-based regulatory approach. In October of 2018 FDA

launched the Plant and Animal Biotechnology innovation action plan. This plan exemplifies FDA's commitment to supporting innovation in plant and animal biotechnology and advancing the technology as part of our public health mission. The overall goal of the action plan is to ensure the safety of plant and animal products using biotechnology while avoiding barriers to future innovation. One of the initiatives outlined in the action plan is known as the Veterinary Innovation Program, also called VIP. The goal of VIP is to facilitate advancements in the development of innovative animal products by providing greater certainty in the regulatory process, encouraging development and research, and supporting an efficient and predictable pathway to approval for both animal cell, tissue and cell- or tissue-based products as well as intentional genomic alterations in animals. It's available for certain intentional genomic alterations in animals and animal cell- and tissue-based products that provide a benefit to animal health and well-being and enhanced food production. It's currently limited to those intentional genomic alterations and cell- and tissue-based products pursuing approval. The VIP offers many important benefits to help sponsors and developers through the approval process. These benefits include access to a toolkit with helpful resources to aid you in the review process, opportunities to discuss alternative data strategies, feedback on development of submissions prior to submission and after conclusion of the review, the ability to stop the clock during the review process to submit data to address deficiencies, as well as hands on how to help for post-approval responsibilities. If you're a new sponsor interested in opening a new file, you can submit your request to participate in VIP in your submission to open a new file. If you have an existing file and would like to request participation, you can submit it to your existing file. If CVM makes a determination that your product does not qualify for VIP, we will inform you in writing within 30 days. If your product does qualify we will notify you in the acknowledgment letter issued in response to your submission and that's sent out by the submission due date.

To determine the overall risk profile of a product we use a risk assessment process. Risk as shown here is the chance or probability of harm to animals, humans or the environment if exposed to a hazard. It's the combination of the likelihood of the occurrence of a harm and severity of that harm. The risk assessment process involves identification of the hazard, characterization of the impact of the hazard, and the likelihood that harm may occur. We look at what risk mitigation strategies in place that could lessen any potential harm. Let's look at a very simplistic example of this. In this risk assessment example, we are determining the risk of catching a cold from my coworker. What is the hazard? This is identified as the cold virus. What's the potential impact? Do I have a compromised immune system? What's my age and overall health status? What is the likelihood that I will get the virus? Do we share an office together? Do we share equipment? Also, am I employing any risk mitigation strategies? Am I washing my hands regularly, using hand sanitizer, and overall reducing exposure to the hazard? We use a similar process when characterizing the potential hazards associated with the introduction of an intentional genomic alteration. For example, when an intentional genomic alteration is introduced we look at whether it is successfully made and whether there are any unintended alterations at the target site or elsewhere. If there are any unintended alterations are they at a location that could impact animal safety or human food safety? Are there any negative impacts of the alteration on either animal or human health? does the alteration or any unintended alteration produce any novel expression products that could impact food safety? What is the impact on the environment? and lastly does it do what it's intended to do? Just because a hazard is present doesn't mean there will be a negative impact on safety or result in a harm. Our risk assessment includes a comprehensive evaluation of all potential risk factors. We do not focus in on one particular aspect. We look at the big picture what the overall sum of risk entails.

Let's look at another example. In this example we are determining the risk assessment for an unintended alteration that's located at the target site or at an off-target location. What is the risk of this unintended alteration causing harm to humans, animals, or the environment? What is the hazard in this case? It's the unintended alteration. What would be the potential impact of that hazard? We look at things like the location of that unintended alteration, the impact of gene expression, and if it is in a known regulatory region of importance. Is it in a location with a known harm such as something known to cause cancer? What is the likelihood of harm to humans, animals, or the environment? What does the animal health data look like? Does alteration increase the fitness of the animals? Are there any new proteins been expressed to impact food safety as a result of that unintended alteration? Lastly, what mitigation strategies are in place that could prevent this? Well-controlled experiments using nucleases with high fidelity and specificity as well as appropriate experimental design can reduce the potential for unintended alterations.

As stated before, not all hazards will result in a harm. We recognize mutations in animals can spontaneously occur in nature and are often benign. We evaluate the impact on safety we consider data that's relevant to the health of the animals, to food safety, and the environment. As shown here we utilize a risk-based approach at CVM. That means depending on the risk profile of a product we may exercise enforcement discretion with no prior data review which means we don't enforce the approval of requirement. We may exercise enforcement discretion with prior data review, or we may require an approval. Where a product goes through the approval process, the data requirements will be proportionate to the overall risk profile of the product using a similar example to what I was showing with the example of the risk assessment process. As science evolves and more information is known about a particular product class or technology, including a better knowledge of the genome and what affects certain alterations may have on its function, it's possible we may be willing to exercise broader enforcement discretion over more products or less data would be necessary to demonstrate safety and effectiveness. Let's look at some examples. This particular example entails a laboratory animal of a nonfood producing species. It's a lab rat with intentional genomic alteration. This is an example of the type of product that poses minimal risk to humans, animals, or the environment. Laboratory rodents are highly contained and likely produced in small numbers. They are also of a nonfood producing species and will not likely enter the human food supply. No data is required to be submitted to the agency for review prior to marketing.

This example is a pig which is an animal from a food producing species that contains a genomic alteration made to mimic human disease and is used for research to develop human therapies. The pigs are highly contained are not intended to enter human or animal food or feed. These animals are produced in small numbers. For this example, you submit data to us prior to marketing that addresses relevant risk factors. We can determine if this is a product for which exercising enforcement discretion is appropriate. To address any potential risks to food safety we look to see if there is a commitment in place not to introduce the animals into the food supply, procedures are in place to ensure they do not enter human or animal feed, and there's an analytical method in place to distinguish these animals from non-altered animals if inadvertently introduced into the food supply. In this example, these animals contain intentional genomic alterations and are utilized for food production purposes. They are minimally contained and are generally produced in large numbers and are intended for food use. Due to all these factors, we would enforce the approval requirement for the genomic alteration in these animals prior to marketing. The requirements would be based on the risk profile of the product including the conditions of use. it would include any unique considerations associated with the alteration such as, are

any novel proteins being expressed? Is the meat from the animals similar in composition to non-altered animals?

We strive to be flexible and we really want to work with you. We are open to proposal for alternative ways to meet the approval requirements for safety and effectiveness. One example of this is with data requirements for genotypic or phenotypic durability, or the stability of the alteration over time. If it isn't feasible to provide data to us for multiple generations let us know why. Genome editing such as CRISPR has made it much easier to make alterations. As a result, you may be interested in performing multiple alterations under one approval. come talk to us about the best way to approach this. Another example where we have demonstrated flexibility is with a recent request for food use for surrogate dams in cattle. These surrogate dams did not contain intentional genomic alterations but gave birth to offspring with intentional genomic alterations. Based on current scientific evidence, through publications as well as previously submitted data, we determined the risk of micro chimerism, or the transfer of genetic material between the fetus to the mother is low. Therefore, per our regulations we determined these animals are not considered to be treated food producing animals and we did not require prior authorization from FDA prior to introduction of these animals into the food supply.

We are very flexible and approachable. We want to talk to you and work with you and learn about your product. My contact information will be provided at the end of the slides. Please reach out to me with any questions you might have. I'll now turn it over to my colleague Judy from CBER who has now arrived. Thank you very much.

XII. Genome Editing for the Treatment of Humans, continued: Dr. Judy Arcidiacono, CBER (slides 15-21)

I am Judy Arcidiacono from CBER's Office of Tissues and Advanced Therapies. I have been involved in the regulation of xenotransplantation products for the past 20 years. So just a little background on xenotransplantation. Pigs are the current animal of choice for use in xenotransplantation because their cells, organs, and tissues are very similar to humans with respect to size and function. The immediate barrier to successful xenotransplantation is hyperacute rejection. That's because of the sugar, galactose-alpha-1,3 galactose, also known as alpha gal, present on the surface of all animal cells except humans and primates. The first genetically modified animals developed for use in xenotransplantation were pigs knocked-out for alpha gal. Now that we have more sophisticated ways to genetically modify animals, multiple genes can be knocked in and knocked out to "humanize" pigs for human xenotransplantation.

Another barrier to xenotransplantation that was identified in early on was the perceived risks associated with Porcine Endogenous Retroviruses (PERV). There are groups out there that have been successful in knocking out genes that prevent infectious PERV expression in donor pigs. This considered to be a mitigation strategy because we're not sure if knocking out pigs for PERV will absolutely remove the risk of infectious disease transmission from other viruses.

When developing genome-edited animals for human use, you will need to talk to CVM first and we will work together at CBER to talk about the transgenes that will be used in the animal. You should provide a clear rationale for the transgenes that you're using. I believe there are up to 13 gene modifications that have been done in pigs, but we don't really know at this point what the most important knock-ins and knockouts are. You would have to provide good rationale for the knocked-in and knocked-out genes. We will need a description of the vector construct, you will need to optimize the genome editing

component, and then we would ask for targeted validation studies. Heather talked about some of the risks in genome editing in animals. We are worried about the off-target effects. The potential for off-target effects might be measured by abnormalities in, or survival of, the animals. However, additional studies will be needed to assess the biocompatibility and function of the xenograft.

I would like to talk about the review team for xeno products. From this slide, you can tell that the review of xenotransplantation products is very complex. For the organ itself (that's what CBER regulates), OTAT is going to use a multidisciplinary review team and I've listed the individuals here and their expertise. We will also go outside of OTAT and include other CBER staff to work with us: the statisticians, CBER veterinary sciences staff, the compliance folks and the GMP manufacturing experts. We will also reach out to other Centers depending on the specific product; for example, if there is a genetically modified animal being used, we will consult with our colleagues in CVM, and from time to time we may use outside government experts.

In this slide, I just wanted to demonstrate how we're going to look at the clinical trial information from the patient perspective. We are going to ask you to provide us with information on the source herd. This is same information you will be providing to CVM. We will be looking for information about the donor pig listed here. Information on processing will depend on the organs, cells, or tissue to be transplanted. We will have to select the right patient, we need to educate their close contacts on the risks of being exposed to animal or human diseases that may have not been previously identified, and the risks of that disease getting out into the public.

With this slide, I just want to show a very simplified view of all the components we're going to look at before you can use any animal, not just a genome-edited animal, in the human transplantation setting. I'm going to pass it off to Laura.

XIII. Clearing confusion about FDA Regulation: Laura Epstein, CVM (slides 37-42)

Hello, my name is Laura Epstein and I'm a policy advisor here at the Center for veterinary medicine, working primarily on the animal biotechnology. Over the years, as we've been involved in regulating this area we've heard from a number of different stakeholders, developers, academia, and others who have an interest in this area. There have been areas of confusion about what our role is and how we regulate; various different questions seem to crop up quite frequently. I will address a few of those now and my colleague, Dr. Ellen Hart, c6an address some of those areas of confusion that apply in the post-market arena as well. The first area is: what is it exactly the FDA is regulating? There's been a lot of confusion about this. Many people say FDA is saying the animal is a drug and we want to clear that up and say no, we are not saying the animal is a drug. The animal is not the product that FDA approves. What FDA approves is the intentional genomic alteration that's in an animal. We have probably contributed this confusion. We have said in the past that, as a shorthand, we will sometimes refer to regulation of the animal. We will try to stop doing that.

Another question we hear frequently is: what is the purpose of FDA regulation? First FDA determines if the intentional genomic alteration is safe for the animal itself. Second, that the alteration and any expression products of it are safe for anyone that consumes food that is derived from that animal. Third, that the intentional genomic alteration is effective. What does that mean? It means, whatever the developer is claiming for that product, it actually does that. If the claim is "this intentional genomic alteration will cause the animal

to be resistant to a particular disease", you need to show that the animal actually is resistant to that disease.

Why does it matter what we intend to do? You heard throughout this webinar previously talking about an intentional genomic alteration. People wonder, what does it matter what I intend to do? What matters is what I actually do. Intended use matters for a number of reasons. It's going to establish what the claim is that you need to support. For example, if you make a broad claim like, "this alteration will cure and prevent all cancer in dogs," then you're going to have to provide to FDA data that shows it does prevent all cancer in dogs. On the other hand, if you had a much narrower claim, like it will extend the life of a dog with lymphoma, then your requirements are going to be a lot more limited. The type of study you design will be smaller and easier to conduct.

We also sometimes get asked if you can say you intend one thing even though you actually may intend something else. You can wave your magic wand and say, "this is my intended use." The answer to that is no. We take a very broad view of what establishes intended use. You will come in and talk to us about what the actual claim is going to be for your product but that's not everything we look at to establish intended use. It includes the communications the developer might have in their printed marketing materials and website. Sometimes if there's a link to something else that makes claims for your products, that can be included in intended use. This is to say, intended use is quite important.

Another common question we hear a lot is why are plants and animals regulated differently? Plants and animals differ in many important ways. There are different laws to regulate them. FDA regulates the safety of plants and animals under different provisions of our statute, the Federal Food Drug and Cosmetic Act. For plants, we look at safety of food from the plant. For animals, we look at food safety, but also we look at safety to the animal. Also, for plants APHIS, which is the Animal Plant Health Inspection Service, regulates plant pest risk under the Plant Protection Act. CVM looks at other risks. We look at risks to the animal and to people that might eat food from the animal under the Food Drug and Cosmetic Act. In addition to that, plants and animals are just different. If you look at the slide, you'll see there's a picture of my dog Ernie and the plant in my office. They are quite different. I will go long periods of not watering my plant and it never protests that. If I were to do that to Ernie, he would make it known very loudly that he does not like that. The point being, animals are sentient beings and plants are not. We evaluate the risk to them differently.

Another thing we hear about a lot is some trepidation about how long this process is going to take. Don't be discouraged by what you may have heard about how long the process takes. You should know CVM follows review timelines that are established under the Animal Drug User Fee Act. We are very transparent about these timelines. They are on our website. I don't have a link here but if you go to the CVM website and you search for Animal Drug User Fee Act, you will find that will come up. Let us know if you can't find it.

In addition to the review time frames there are a whole host of other factors that affect how long an application takes. For example, how early a sponsor may open an investigational file. With these biotechnology products, in general, sponsors tend to open files much earlier than they do with traditional drug products. If you open a file early in the development process and you're working on research and to refine the product, then it can take a long time from the opening of that file until you actually get an approval.

Another thing that can affect the timeline is the complexity of the product. If it's a nonfood animal, then food safety is not going to be a component of the review. If you have an animal that's intended purposely for open release into the environment, then that's going to mean there's a need for more data submitted on environmental consequences that we review under the National Environmental Policy Act.

Another thing we found in the past that can affect the timeline is the level of public interest in a particular product. If we hold public meetings or sometimes if we open a docket for public comments, that can affect the timeline because we get a lot of comments on these issues. It takes time to go through those comments and consider them all. All of which is to say what you hear about one particular product is not reflective of the timeline for another product because there's always different factors that come into play.

Lastly, we should mention that CVM has a review process that's known as phased review, and what this means is that instead of a sponsor coming in with one huge application at once, under phased review instead they can submit sections of the application as they are completed on a rolling basis. This benefits the sponsors and FDA CVM because it allows us to work together through the process and in an interactive way and provide input as we go along. It does mean sometimes there can be a really long lag between submission of different sections. A sponsor may submit one section that's completed, and they may have a long way to go to put together the data for another section. They may be in the process of doing that research. Sometimes those are the things you can't know when you hear about how long an application has taken. Don't be discouraged by it. Come in and talk to us and hopefully you can get a realistic sense of how long it will take for your particular product. I'm now going to turn it over to my colleague.

XIV. Post-approval: Dr. Ellen Hart, Office of Surveillance and Compliance (OS&C), CVM (slides 43-47)

Thank you, Laura. Thank you for joining us today. My name is Ellen Hart and I'm a veterinarian from the Office of Surveillance and Compliance at CVM. My job is to offer clarity on areas of confusion related to post-approval. Let's get started. My company got an intentional genetic alteration in an animal approved by FDA. Why do we need to do things post-approval? The goal of post-approval monitoring is to continually monitor safety and effectiveness of an approved product over its lifetime. Before approval, it is likely that you experienced several changes to your production processes when you transitioned from a controlled laboratory setting to a field trial or scaled up your production. Post-approval, you will likely be producing on a larger scale. Ongoing monitoring helps ensure that the approved alteration or alterations in these animals continue to be safe and effective by providing early identification of any unanticipated changes and helps maintain public confidence. Like Heather mentioned earlier, we appreciate that one size certainly does not fit all. Part of our flexible approach that was mentioned earlier is to work with you to leverage the work you've already done during the approval process and what you're currently doing internally to ensure that after approval the product continues to be the same safe and effective alteration or alterations that you worked with us to get approved.

We've heard from concerned farmers and producers wondering whether they will have to register with FDA. In general, our post-approval monitoring requirements are geared towards companies, which we refer to as sponsors, manufacturing and distributing animals with alterations rather than towards farmers, producers, or consumers that may use, raise, or eat them. So, just because a farmer is raising animals with intentional genomic alterations, that does not make that farm a drug manufacturing facility. Farms with animals containing intentional genomic alterations on the premises do not have to register

with FDA, although exceptions might include an instance where a farm is owned by a sponsor or company.

For animals with intentional genomic alteration, adverse events or experiences might include an absent or incorrect alteration or if an animal is found to be susceptible to a disease for which it is intended to be resistant. For example, if chickens genetically altered to be resistant to avian influenza get avian influenza, that would be considered an adverse drug experience (or ADE). Other examples might include unexpected malformations or increased mortality rates. It's the responsibility of the sponsor to report adverse experiences to FDA, but reporting is voluntary for a farmer who's raising animals with genetic alterations on a farm. We would, however, encourage farmers to voluntarily report adverse experiences to either the sponsor or FDA because, although there are no requirements for farmers to report, it's valuable to know what their experiences are with these animals.

And finally, do I need a new FDA approval to use conventional breeding practices on my farm? Since this is my final slide, I'll leave you with my shortest answer yet: no. When you breed animals containing intentional genomic alterations with other animals using conventional breeding practices, you do not need approval. For example, this might include breeding animals with genomic alterations with one another or with wild-type animals.

Like everyone else who has spoken today, we have an open phone policy. If you have questions or something doesn't make sense, please do not hesitate to reach out. We look forward to getting to know you and your products throughout the approval process and are excited for the opportunity to share a vested interest in human and animal health with you. With that I'll turn it back over to Laura to finish out the webinar part.

XV. Clearing confusion about FDA Regulation, continued: Laura Epstein (slide 48)

One last area of confusion to cover now, and then you can tell us your questions about what areas of confusion we did not cover. Heather mentioned before the flexibility of our system and we want to be as flexible as we can be within the law. One area people have been somewhat confused about is with respect to guidance documents; whether a guidance document establishes requirements. Guidance documents interpret laws whether from a statute or a regulation. To the extent a guidance document is referencing something that is included in statute or regulations, these in fact are requirements, but the requirements are not established by the guidance. It's the statute and the regulations that establish requirements. What the guidance does is to interpret the requirements under the law. These interpretations will say "here's the requirement in this regulation and here's how we interpret that requirement for your particular type of product". That interpretation is not a requirement. If you see our interpretation of the requirement and you think this is not going to work for my product, that's where the flexibility comes in. We want you to come talk to us and tell us "this does not work for my product and here's why it does not work". We can work with you to find an alternative approach that will still meet the regulatory requirements. We hope that will help with some of the areas of confusion we tend to hear about a lot.

This is our contact information. You can use the "Ask CVM" mailbox for any type of inquiry. If you're not sure where to go, if it's a CVM inquiry, you can send it there. We put under it our general biotech CVM mailbox, which for any questions that have to do with what you heard today would probably be appropriate to send there. We also have the contact information for Heather and me and our project manager Sarah, and we can put you in

touch with other people as well. And the CBER mailbox, if you want to contact with the genome editing questions for them. We're going to leave this up during the break.

We're going to take a 10-minute break. When we come back, we will have a Q&A session. We received a lot of questions in advance. We will address a lot of those when we come back. Also questions you've been submitting during the webinar. You can keep submitting them during the break and we'll do as much as we can when we come back in 10 minutes. If you miss something in the slides, you should know we're going to be posting a recording of this webinar and a transcript from it. It may not get up right away. Eventually it will be there. Thank you. [The event is on a 10-minute recess. Captioner on standby]

XVI. Question and Answer Session: All speakers (slide 49)

We are now going to have a Q and A session. We do feel like we probably addressed a large portion of the questions with what we covered in the rest of the webinar. We're going to stick to questions mostly related to what the scope of this webinar is, not about Guidance 187. If you have questions specific to your product and that are in the weeds, we encourage you to talk to us about it, rather than pose those questions now. One last thing before we start with the questions that Heather wants to ask folks to give us some feedback on.

I'd like to request your feedback, first of all, on the webinar we presented today. Hopefully you were able to write down our contact information. It will also be posted later. Send us any feedback you may have about the webinar. Also, we are considering the possibility of future webinars. One of the ideas we had was related to the next generation sequencing methods that Dr. Stella Lee mentioned in her presentation. We thought we could go more in depth into those. Let us know what you think of that proposal and send us an email and let us know if that is something you would be interested in. Or you can type it into the comment box.

I just want to reiterate that CBER has an open-door policy like CVM. Come talk to us early and often. We wouldn't want you to waste time and money doing something that won't be appropriate.

Q1 Please address the potential for pathogens jumping the species barrier when pig organs are engineered to contain more human proteins and their organs are then transplanted into humans.

A1 Judy Arcidiacono: One of the approaches for xeno transplantation is mitigating risks. So to mitigate this kind of risk, the best we can do is monitor the animal herd, the source animal and human recipient for potential pathogens. So we expect you to harvest and date samples from the donor herd, the donor pig, the recipient, and then, over time, continue taking samples from the recipient and storing them so that if something comes up, some adverse reaction or some virus that's identified in a particular recipient or other recipients, we can go back and look. That's really the best we can do at this point in time.

Q2 What the recommendations for surveillance of the genetically altered source animals if the offspring is the focus of a biotech product for xenotransplantation?

A2 Judy Arcidiacono: If you remember the slide that I showed the pig herd, the individual pig, and the processing and the patient. Early on, until we have a better

grasp of what the risks are, we would expect surveillance of the herd (so, a sentinel animal). Then quarantine of the pig that will be actually the donor source. Then again, the banking of samples and screening before transplantation. Of course, you can't screen the animal once we've harvested the organs, but continuous screening of the herd in case something comes up post-transplant.

Q3 Will animals containing small, precise, non-transgenic edits (for example, deleting less than 50 bp) be regulated differently than transgenic animals, or animals with larger deletions?

A3 Heather Lombardi: I think we made it clear in our slides that we use a risk-based approach to regulation and as Stella explained the size or location of the alteration doesn't necessarily correlate with risk -even small deletions have been known to cause potential safety concerns. We don't regulate these modifications differently in that we determine how much data is required to support safety and effectiveness based on the risks posed by the specific alteration.

Q4 What kind of resources exist that can help expedite the review process for approving GE animals?

A4 Heather Lombardi: We don't have an expedited review process, but as Laura mentioned, we have specific timelines which we work under according to the Animal Drug User Fee Act or ADUFA. Also, we have programs such as VIP to help facilitate the efficiency and transparency of the regulatory process.

Q5 How involved is CVM in INTERACT meetings for xeno products that involve an animal with gene editing components? What information would CVM like to see in these types of INTERACT packages?

A5 Heather Lombardi: I'm going to ask for Judy's help on some of this. Let me explain and then Judy can add anything I might have missed. INTERACT involves early conversations with sponsors at CBER during development or the pre-pre-IND stage. For products that involve both Centers, CVM and CBER, CVM is invited to participate in those meetings. At those meetings, we remind sponsors they have CVM requirements they need to fulfill, and we invite sponsors to come in and have a specific meeting with us to talk about those requirements. However, the focus of the INTERACT meetings is to focus on the CBER requirements.

Judy Arcidiacono: I would say we have a collaborative review process. They include us in their pre-meetings. The INTERACT program is just another name for the pre-pre-IND. We ideally would like to talk to CVM at the same time have them place to have them place. It's appropriate whether the animals and ideally for license biologic we would like to have that logic. Primarily in your licensure CVM you will be required to follow the animal. I guess it's to monitor the animal. That's not CBER's provisions. It will be important have access to information.

Q6 What types of gene edits fall under GMO regulations?

A6 Heather Lombardi: We typically don't classify edits of GMO or non-GMO. We actually focus on the product of the alteration rather than the technology itself. The particular requirements are based off those risks.

We've received two questions that get to the same thing.

Q7 How will intentional alterations that are indistinguishable from existing natural variants be monitored in imported animal products from countries where they are not treated as a GMOs.

Q8 How will the FDA interpret/regulate the import of gene edited animals from other countries where gene editing is not regulated if the gene already exists in the target species?

A7&8 Laura Epstein: I don't need to read both of them; both of them have to do with imports and how do we handle imports and if there's a different status. There's a process CVM has for where someone has to import food products from a country where they were treated with an animal drug that is approved or legal to use in that country but not approved in this country. That's called establishing an import tolerance and what it comes down to is the food safety portion that we would do for a full approval package. Whether you have an approval or a tolerance, generally we require a method to detect the genomic alteration. What we say is it's a practicable method. If there's some reason you can't develop a method, we can establish an import tolerance without that method and we can find alternative ways of identifying those products, for example through recordkeeping.

Q9 How will the FDA work with the US Fish and Wildlife Service to enable applications of biotechnology for conservation which are not related to medical or agricultural purposes?

A9 Laura Epstein: We communicate with several other agencies where we have either concurrent jurisdiction or where jurisdiction overlaps, and we have an interest in the same products. We work with CDC, EPA, USDA, and the US Fish and Wildlife Service. It doesn't matter if it's an agricultural use as we said. You just need to demonstrate it achieves whatever it's claimed.

I have the next question.

Q10 Gene drives change the rule of mendelian inheritance. How are these elements regulated?

A10 Heather Lombardi: We regulate these products like any other product in that we look at the specific risk profile of the product with regards to what data might be required. Obviously with something like gene drives, environmental can be a very critical component.

Q11 What are CVM's expectations for target animal safety evaluation for biotech in animals?

A11 Heather Lombardi: We look at target animal safety by looking at the overall health of the animals and we compare the health of these animals to those of their counterparts that do not contain alteration.

Q12 If a company does editing on an animal that's already been edited once and approved, what additional safety testing would be required?

A12 Heather Lombardi: I think this is getting at if the same edit is repeated. If a sponsor wishes to make an edit more than once we would entertain that under a

single approval and work with the sponsor to address how to demonstrate the different edits are being made consistently and are also safe and effective.

Q13 Is the FDA coordinating with Canadian regulatory agencies regarding synchronous approval?

A13 Heather Lombardi: FDA is interested in working with our international regulatory counterparts including Canada. If you're interested in that type of interaction, please let us know. We'd like to consider leveraging data that will be provided to both regulatory agencies where possible. You would need to give us permission to do that, so we can discuss the contents of your file.

Q14 Will meat or other animal derived products from genome edited animals be required to be labeled to consumers?

A14 Laura Epstein: This is largely regulated by the USDA. Food that comes from animals that have intentional genomic alterations and falls within the scope of USDA's recently issued regulation for labeling of foods with bioengineered ingredients would have to comply with that regulation. For animal-derived products, that includes most fish. Meat, such as beef or pork or poultry, would not fall under the scope of that regulation but the labeling is regulated by USDA. You need to talk to them about that.

Q15 Will every single animal that has an altered genome be individually evaluated or will all animals with same intentional alteration be considered as a group?

A15 Heather Lombardi: When we look at the safety and effectiveness of an intentional genomic alteration we don't focus on one particular animal. We look at the entire lineage of animals that will contain alteration.

Q16 Are sequences made to mimic those of the same species considered differently from genes originating in other families or kingdoms?

A16 Heather Lombardi: I talked about our risk-based approach to regulation. We evaluate each product based on the specific risks it poses. There may be unique risks to modifications involving a sequence from another species or family that doesn't exist for sequences coming from the same species. Even alterations designed to mimic naturally occurring sequences can still have their own risk. As we learned from Stella's presentation, nucleases sometimes do not only cut in the site they are intended to. Sometimes it cuts in other places and sometimes even when they cut at the right place that repair is improperly made. There can be inherent risks associated with the alteration even though it's meant to mimic a naturally occurring sequence.

Q17 Is animal welfare taken into consideration in regulating genome editing?

A17 To the extent that animal welfare encompasses animal safety, the answer is yes. In reviews, we look at the physical health of the animal and, to the extent it can be measured, we look at behavioral health of the animal.

Q18 Why isn't an offer made by FDA to applicants with products eligible to participate in the VIP program? FDA can assess the applications for those

that would be eligible for the VIP and then ask the researcher if they wish to apply or participate. New applicants aren't going to know the process ins and outs to know they should be included in the VIP program.

A18 Heather Lombardi: Thank you for your comment. We have reached out to the sponsors we were aware of and let them know about the program, but also for new sponsors, when you request a new file with us, there's a question in the eSubmitter template that asks if you're interested in VIP participation. That lets us know if you want to participate in VIP. Hopefully this process it isn't too burdensome.

Q19 Do you consider the inherent value of the final product in the evaluation? Example: A new treatment for a human disease versus a cosmetically enhanced animal for human enjoyment.

A19 Laura Epstein: No. The answer is your claim is what you have to prove. We don't decide how worthwhile the claim is. That's true of all FDA regulated products. There are human drug products and devices that are for cosmetic purposes where we don't make value judgments and it's the same for these products. If there's so-called cosmetic enhancement, you have to demonstrate it does that. That said, if you're making some cosmetic enhancement to dogs that has a very significant impact on their health, that's going to weigh in to the evaluation because you still have to show the product is safe for the animal.

Q20 You request public input. Why do you request it when the people most likely to give input are not well-informed and not scientists?

A20 Laura Epstein: I'll fess up here. I'm not a scientist. I've been working on this a long time, so I hope I have a little idea what I'm talking about. The answer is we can't always request input. We have some limitations because of confidentiality concerns. When we have an application, that is considered confidential information. Even if they open an investigational file, that in and of itself is confidential. We cannot admit or deny a sponsor has opened the file unless they have done so publicly. We are limited in what we can do in terms of public input without the sponsor's agreement. There are a lot of sponsors that recognize the need for public acceptance so they're willing to make a lot of information public and work with FDA to gain some public input. Public input can benefit FDA by getting more information and the public by learning more about it and being able to gain confidence in the product and in FDA's review of it.

Q21 Who will regulate, and under what framework, genome-edited insects, arthropods, or mosquitoes.

A21 Laura Epstein: This is a little complicated. With respect to mosquitoes, we did put out a guidance document. Go to the CVM website and search for mosquito-related products and you will find that document. Basically, it says if you have a product that is intended to control the population of mosquitoes by killing them or limiting their reproduction, those types of products are regulated by EPA. If, on the other hand, you're making a health claim… It could be the same product. You're limiting the population but you're saying this product will limit the transmission of Zika virus by mosquitoes or some other mosquito-borne disease. That type of claim comes to FDA. That's another good example of why intended use can be important. As far as other insects are concerned, APHIS regulates a number of insects that are genetically altered that have plant pest risks. They are regulating a diamondback

moth and some others as well. If you have that type of product, you go to APHIS. If you have questions, submit your questions to the website on the contact page and we can sort out whose jurisdiction it is.

Q22 Will various strains of mini pigs that have been bred for research and never intended for food eventually be considered non-food species?

A22 Laura Epstein: No. I've been talking about intended use but there's no element of intended use in the food definition. Food is food. You don't have to intend it to be food. If you have a pet pig that you're keeping, that is still considered to be a food animal. A pig is a food-producing species. The same is true for an IGA in an animal developed for biopharm purposes. We still consider them to be food producing. Something that does play into the food safety review is what controls there are to prevent the animal from going into the food supply if that's not what you intend. They're highly contained. It's a food-producing species, but the safety review may look different.

Heather addressed gene drives.

Q23 If an IGA is used to alter an animal for use in the production of animal biologics, would FDA have oversight even though the resulting product is regulated by USDA APHIS?

A23 APHIS regulates animal biologics. The Center for Veterinary Biologics is part of USDA APHIS. If you have an IGA in an animal that's altering the animal, so it would then, for example, produce an animal biologic in its milk or egg, that would work the same way as with the biopharma animals that produce human products. FDA would regulate the IGA in the animal and APHIS would regulate the product derived from the milk or egg of that animal if it's a veterinary biologic. If, on the other hand, you had an IGA in the animal that met the definition of a veterinary biologic, then that would be regulated by APHIS CVB.

Q24 Will it be necessary to get an approval for an animal producing cells, tissues, or organs or will the agency be exercising enforcement discretion on those animals if they do not enter the food supply.

A24 Heather Lombardi: I want to guess that what this question is getting at is related to xenotransplantation products. In this case, you would have intentional genomic alterations that are then used as sources for cells, tissues or organs to be used in human medicine. The answer is similar to some of the answers I've given. It's based on the risk of the product. As these are being used for something very important for human medicine, currently we are requiring approval for these types of products.

I must've done a good job with post approval stuff because this is the first question to come up.

Q25 Why is there a different standard requirement for facility registration for a sponsor's facility that is specifically for growing, not manufacturing, the animals compared and any other farm that is just growing the animals for production?

A25 Ellen Hart: So if you'll note in my presentation, I did say 'may' in part because every product is going to be a little bit different. But in probably the most profound way this is actually beneficial. So part of how post-approval is laid out, is that every adverse event that comes into a sponsor would have to be reported to us. And if it's a sponsor-owned facility, that would mean every adverse event would have to come to us. And it's actually useful for both us and you to cluster those into something very meaningful. So that's basically what we try to do there is to cluster them into something meaningful so that we can use it and it's useful to you, and that you don't have to report every single adverse event to us. So that's probably the most meaningful way that that's beneficial.

Q26 To follow up on the import question, if the gene edit (example: a small deletion) is not regulated in a country and therefore enters into general production, how will FDA even know it's in an imported product?

A26 Laura Epstein: You can ask that question about a whole lot of FDA-regulated products. The reality is, unlike Santa Claus, we're not all-seeing and all-knowing. We can only find what we know to look for. That's true of traditional drug products and all sorts of products. What we do is do our best to communicate with our international partners. We have ongoing conversations with them. Our enforcement folks have offices around the world. We follow the science. People are publishing all the time on what they're doing. We try to keep our finger on the pulse of what's going on. We have a good sense of what's happening. As a general matter, these products are really new and they're not slipping in under the radar in other countries. They pay attention to them. It's covered in the news. We're going to continue to pay attention to it. That's our best method of knowing what's going on out there. I would encourage those working in other countries to come to us early to have conversations in advance and make sure there's not going to be any holdup. If you want to import products, we would really like to facilitate a seamless process. We can't do that if you don't come to us and talk to us about it. If we find out about something as you present it at the border, that will hold things up. But by meeting and talking to you when you're in the process it won't hold things up.

I think we're just about out of time. We would like to thank you all for joining us for this webinar. We hope it's been informative and as we said this is not the end of the conversation. We want to delve into other topics. Some of them are more specialized because the science is evolving very quickly. We think it would be helpful to have more an exchange of information about all this. Follow up with us if you have additional questions or you would like to talk to us about your particular products. Thank you.

[Event concluded]