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Regulatory Considerations for Using Pharmaceutical Products in Research Involving Laboratory Animals

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Slide 1 (Regulatory Considerations for Using Pharmaceutical Products in Research Involving Laboratory Animals)

>> *Babcock:* Today is June 4th, 2015. I am Dr. George Babcock and it is my pleasure to welcome Dr. Dorothy Bailey and Dr. Neal Bataller from the FDA Center for Veterinary Medicine to the OLAW Online Webinar series to present **Regulatory Considerations for Using Pharmaceutical Products in Research Involving Laboratory Animals**.

Dr. Bailey is a Program Head for the Index of Legally Marketed Unapproved New Animals Drugs for Minor Species at FDA's Center for Veterinary Medicine. She joined the FDA in 2006 as a Veterinary Medical Officer working on new animal drug approvals. She moved to the Office of Minor Use and Minor Species Animal Drug Development in 2008 and helped establish the Indexing Program, which is an alternative to the approval process for certain minor species drugs. Prior to joining the FDA, Dr. Bailey completed a large animal medicine and surgery internship and worked as a laboratory animal veterinarian at a contract research organization.

Dr. Bataller is Director of the Division of Surveillance at the Center for Veterinary Medicine. In addition to being a veterinarian, he has graduate training in veterinary clinical nutrition, epidemiology, and biomedical engineering. With the exception of a short stint at the USDA Animal and Plant Health Inspection Service, he has been with the Agency since 1993. During that time, he has had a primary lead for a number of various programs and issues, including adverse event reporting, compounding, monkey pox, melamine in pet foods, drug residues in meat and milk, and BSE (or mad cow disease). He worked on many of these issues while serving as Director of the Division of Compliance. His present Division is involved with all matters related to marketed animal drugs and devices, including the oversight of all approved animal drugs. His Division is also responsible for overseeing the sales and use estimations of antimicrobial drugs for food-producing animals.

We're also pleased to have our colleagues Dr. Carol Clarke from USDA, APHIS, Animal Care and Dr. John Bradfield from AAALAC joining us today. Susan Silk and Dr. Axel Wolff will represent OLAW in today's webinar. Let's hear first from Susan Silk, the Director of Policy and Education at OLAW.

Slide 2 (The Terms "Pharmaceutical- and Non-pharmaceutical-grade Substances")

>>*Silk*: Hello, everyone. This letter shows the first time the terms pharmaceutical-grade and non-pharmaceutical-grade were used in the animal research community. The letter was written by Nelson Garnett in 1993. Dr. Garnett was the director of the Division of Animal Welfare of OPRR [Office for Protection from Research Risks, now OLAW]. I know that as soon as this webinar ends all of you will get out your microscopes and read this letter. And when you do, you will find the origin of the language that OLAW and USDA use today.

The terms pharmaceutical-grade and non-pharmaceutical-grade are also used in the *Guide*, [[Guide for the Care and Use of Laboratory Animals](#)] however, these terms are not used by our colleagues at the FDA who are responsible for protecting the public health by assuring the safety, efficacy and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics and products that emit radiation. And that's not all they do. Their mission statement goes on for two more paragraphs. I invite you to go to their Web page and read all of their many [responsibilities](#).

Slide 3 (Bridging Our Terminology)

The reason for our webinar today is to learn about the area in which the authority and responsibility of the IACUC overlap with the much broader responsibilities of the FDA. Our guest speakers will explain the FDA's regulatory authority and language. Then OLAW, USDA and AAALAC, will explain how this information impacts and influences the expectations of our organizations. We do not intend to change our terminology. We will continue to use the terms pharmaceutical and non-pharmaceutical. And I hope that after this webinar all of you will have a better understanding, a bridge, if you will, between our

oversight language and the language that FDA uses. On March 1st, 2012, OLAW, USDA and AAALAC recorded a webinar called **Use of Non-Pharmaceutical-Grade Chemicals and Other Substances in Research with Animals**. That webinar has been archived [[Policy and Guidance Archive](#)]. It will be replaced by a recording of today's webinar. We have also updated OLAW [FAQ F4](#). We will not answer questions live today so that we can use all of our time for lecture and discussion.

Dorothy and Neal are going to present a lot of information. Don't worry if you're not able to write everything down. OLAW will post the webinar recording, transcript and slides as soon as we can. That may take us a couple of weeks. I'm sure that you will have many questions. Please email your questions to the address shown on the slide [olawdpe@mail.nih.gov] and today's presenters will work together to answer them. OLAW will then post the questions and answers when they're ready, probably in July 2015. And now, Dorothy, it's your turn.

Slide 4 (Regulatory Considerations for Using Pharmaceutical Products in Research Involving Laboratory Animals)
>>*Bailey*: Thank you, Susan.

Slide 5 (Today's Topics)

In the FDA portion of today's presentation we're going to talk about investigational use of drugs, clinical use of drugs, extralabel drug use, drug compounding and euthanasia.

Slide 6 (Definitions)

I'd like to start with a couple of definitions just to help clarify what I'll talk about in the presentation. First when I talk about test article, I mean where the drug that you're administering is the focus of your research. When I talk about clinical use, it's essentially any other use that isn't test article use. In general, a drug administered for this use is in the care of an animal or population of animals. When I talk about MUMS, I mean Minor Use & Minor Species. In terms of FDA regulation, there are seven major species in the United States, and they are horses, dogs, cats, cattle, pigs, chickens and turkeys. All other animals, excluding humans, are considered minor by the FDA. And when I say minor use, I mean a rare disease or condition in one of the seven major species.

Slide 7 (Investigational Use (Test Articles))

Now I'm going to talk about investigative use of drugs, and once again this is where the drug is the test article or focus of research. And to help explain FDA regulation of investigational uses I've split it into three categories. The first category is basic research. This is where a drug -- essentially at this point it's a chemical or compound -- is being studied and it's prior to any sort of known use of the compound as a drug. So, this is prior to drug development. This type of test article research is not reported to the FDA.

The second category is pilot or preclinical studies that are conducted early in drug development. At this point there is a known use for the compound and it's a drug use.

I've provided you with the citations to the Federal regulations which cover this type of use for both human [21 CFR 312] and animal [21 CFR 511.1(a)] drugs. Essentially what these regulations say is as long as the drug is labeled appropriately as an investigational drug and certain shipment records are kept, the drug manufacturer can ship the drug interstate and interstate commerce and the drug can be used in studies involving laboratory animals. These studies do not have to be reported directly to the FDA.

The third category of investigational use is use under an Investigational New Animal Drug (INAD) file. This is for an animal drug. At this point, drug approval is being pursued, a file has been opened with the FDA, and use under this investigational file is limited to collection of data to support approval or conditional approval. This data will be submitted to FDA for review.

Slide 8 (Legal Choices for Clinical Care of Research Animals)

Those are the three categories of investigational use or test articles. Now I would like to talk to you about clinical use of drugs in research animals. Once again, this is any use that is not a test article use such as providing anesthesia to do a procedure on a research animal during a study or providing analgesia after the procedure. Your legal choices for using a clinical use of a drug in research animals are using an approved or conditionally approved drug, using an indexed drug, using an approved drug in an extralabel manner, and using a compounded drug made from an approved drug.

I am going to talk to you about approval, conditional approval and indexing, and my colleague Neal Bataller is going to talk to you about extralabel drug use and compounding.

Slide 9 (Approved Drugs)

When available, you should always use an approved drug. The reason you should use an approved drug is because well-controlled studies have been conducted to support target animal safety and effectiveness. Manufacturing studies have been conducted to demonstrate the strength and purity of the drug and these studies have been submitted to the FDA and reviewed by FDA scientists prior to the approval.

Approved drugs are manufactured in accordance with Good Manufacturing Practices or GMPs. This ensures the quality and consistency of the drug. So when you use the drug you have confidence that what you're using that it is what it says it is. We understand that it's difficult many times to use an approved drug in laboratory species because there are not many drugs approved for the species that are typically used in laboratory research. This is where extralabel drug research can be very beneficial for you. As long as certain requirements are met, you can use an approved human or animal drug in an extralabel manner and you still have the confidence that you're using a drug that has been reviewed by the FDA. Neal will go into the specifics of extralabel drug use later in the presentation.

Slide 10 (How to Recognize Approved Drugs)

You can recognize an approved drug -- they do not always have an application number, but they may have a new animal drug application or NADA number or an abbreviated new animal drug application, an ANADA number. These will be six digits and an ANADA number will start with a two. If you're using a human drug in an extralabel manner, it may have a NDA number on it.

If you don't see an NADA or ANADA number, we do have a searchable database of approved animal drugs on the FDA website at [animal drugs at FDA](#) and we've provided the link here. You can also go on to the FDA website and find the FOI summaries or [Freedom of Information summaries for approved animal drugs](#).

These summaries are basically a brief summary of all the information that the FDA reviewed in support of the approval. And please note that these summaries are listed by the NADA or ANADA number, so you would need to know that information before you went to this database.

Slide 11 (Finding Information About Drugs)

We received a question prior to the webinar asking how one can find detailed information about drugs and their formulations. In addition to the two resources I just told you about, there's also the [DailyMed](#) website, which is by the National Library of Medicine. It provides labeling information for both human and animal drugs.

Slide 12 (Conditionally Approved Drugs)

The second option for an approved use, clinical use of a drug, would be to use a conditionally approved drug. Conditional approval was created by the Minor Use and Minor Species Animal Health Act of 2004 or what we call the MUMS Act. Conditional approval is only available for a minor use in one of the seven major species or a drug for use in a minor species. All approval requirements must be met to the current standard except for effectiveness. The FDA has to have determined that there is a reasonable expectation that the drug will be effective. These standards have to be met prior to conditional approval. Once the conditional approval is granted, the drug can be marketed for up to five years while the sponsor completes the effectiveness section to complete the approval. Please note that extralabel use is prohibited of conditionally approved drugs.

Slide 13 (How to Recognize a Conditionally Approved Drug)

The labeling of a conditionally approved drug should have an application number on it and it would be a CNADA number that would be six digits long. It is important to note that conditionally approved indications cannot be combined on the same label as an approved indication. So if you are using a drug with a CNADA number on it, you know that the indications on that label are conditionally approved. There are no approved indications on that label.

Slide 14 (The Index of Legally Marketing Unapproved New Animal Drugs for Minor Species (Index))

The third legal status for a drug or an animal drug is indexing or the Index of Legally Marketed Unapproved New Animal Drugs for Minor Species. Indexing was also created by the MUMS Act and it's an alternative pathway to legal marketing status for certain minor species drugs. These drugs can only be used in non-food-producing minor species or certain early life stages of food-producing minor species. When we say early life stage, we mean a completely separate life stage such as fish eggs and oyster spat. I've provided you with a lengthy definition for food-producing species and the FDA uses this definition to determine if a minor species is food-producing for the purposes of indexing. But in short essentially it is food-producing if any number is bred or harvested to have edible products commercially distributed for human consumption or consumption by food-producing animals.

Slide 15 (Food-producing Species)

It's also important to note that it does not matter where the animal lives. If it is considered to be food-producing, then indexing is prohibited. As an example, rabbits are considered to be food-producing in the United States. So even if the rabbits are housed in a laboratory and used for research, use of an index product would be prohibited.

Slide 16 (Adding a Drug to the Index)

Adding a drug to the index is a three-step process and it's much faster than an approval. The first step is when a drug manufacturer, or we call them an indexing requester, submits a request for determination of eligibility to the FDA. This submission includes drug information such as intended use, conditions of use, and known contraindications. They also have to submit a summary of the manufacturing process. This is much less onerous than the manufacturing studies that have to be conducted to support an approval, but the summary does have to be detailed enough that the FDA knows that the manufacturer understands Good Manufacturing Practices and will be able to use them when they manufacture the product. They also have to submit safety information outside of the target animal safety, so this would include environmental safety and human user safety.

Slide 17 (Adding a Drug to the Index)

If the FDA determines that the drug is eligible based on this information, the second step in the process is selection of a qualified expert panel. The target animal safety and effectiveness information for an index drug is reviewed by an outside expert panel, not by FDA scientists. This panel must be at least three members and they must be qualified by training and experience to review the target animal safety and effectiveness information. The panel members cannot have a financial or other conflict of interest that would influence their decision and they cannot be employees of the FDA.

Slide 18 (Adding a Drug to the Index)

If the FDA approves the panel, the panel then convenes and they review all of the available target animal safety and effectiveness information and this information can

include study data if available. It also can include literature. They can even use their own experience using the drug to support their decision on whether the drug is safe and effective. The expert panel then writes up a written report of their findings. This report is submitted along with a draft FOI summary and draft labeling to the FDA and the request for addition to the index, which is the third and final step of the process. The expert panel must be unanimous in their decision that the drug is safe and effective for the intended use. If the FDA agrees with the expert panel findings, we will put the drug in the Index.

Slide 19 (Indexed Drugs)

The holder of an indexed drug signs a commitment to manufacture the drug following Good Manufacturing Practices. Index drugs also have the same reporting standards as approved drugs, and this is for the entire life cycle of the drug. So once it's indexed or approved, they have to report adverse events to the FDA and also to report marketing information on an annual basis to us.

And please, also note very importantly, that extralabel use is prohibited for indexed drugs. For this reason, when possible, we try to make the indications on an indexed drug as broad as possible so we do not restrict use.

Slide 20 (How to Recognize an Indexed Drug)

The labeling for index drugs will have a Minor Species Index File number on it, this is a MIF number. This is a six digit number and it will begin with a nine.

I also want you to know that currently indexed products have, in very bold print, "Not Approved by the FDA" on the label. We are currently working to amend the law so we can remove this language from the labeling, because we think that it's a disincentive to drug manufacturers to have their product indexed and we think it can be very confusing to the user. We want you to know if you use an indexed product as of now you will see this language, but as long as it is followed with legally marketed as an FDA indexed product and it has a MIF number that it is a legal drug and as long as you use it by the label you are using a legal drug.

Slide 21 (Indexed Products List)

The [Index](#) is maintained on the FDA website and each Index listing has a link to the FOI summary and the labeling for the drug product. We just started the indexing process in 2008, so it's only been seven years, and we already have 10 products on the Index. And just for comparison, it can take up to 10 years to get a single drug approval. So we feel like the process is working and we are getting drugs legally available as quickly as we can.

And to let you know, there are two different extended release buprenorphine products on the market for laboratory rodents. One is for rats and the other is for rats and mice. Unfortunately neither of these products is currently available, but the manufacturers of the drugs are working to get them back on the market.

Slide 22 (What You Can Do)

And lastly, I would like to talk about what you can do. This process is well-suited for drugs for use in laboratory research, for clinical use in laboratory research, I should say. And honestly, indexing was created to help with legal drug status for animals like laboratory animals. Congress knew that there was an issue, that there were not enough legal drugs available labeled specifically for these animals, and the answer was to create the indexing process.

If you have a product that you need, contact the manufacturer and suggest that they have it indexed. You could also offer to sit on an expert panel and provide your expertise in reviewing the target animal safety and effectiveness for an indexed product. And I've provided my contact information here [Dr. Dorothy Bailey at 240-402-0565 or Dorothy.bailey@fda.hhs.gov]. If you have any questions about indexed products or you know a drug manufacturer who is interested in having their product indexed, please feel free to contact me and I will do the best I can to help. And now I'm going to hand this over to Neal.

Slide 23 (What is the Difference?)

>>*Bataller*: This is Neal Bataller. I'll build on what Dorothy had been talking about. My angle is going to be more on what is legal versus what is not legal. Just so people have an understanding. I'll also touch on euthanasia policy, products, and then give you an overview of when it comes down to what our enforcement priorities are.

So the first thing I would like to touch on is these important distinctions between a law, policy, regulation and case law. So the law is an act of Congress, the legislative branch. And only they can put laws forth, the executive branch can't really even recommend laws. Only Congress does that. And they put forth the federal Food, Drug and Cosmetic Act, basically what we operate under in addition to some other laws or statutes. They will enact other laws and statutes that amend this. A regulation is something put forth by the executive branch, in this case the FDA and that kind of executes the law. Sometimes the law isn't very practical for implementation, so a regulation will implement the law. It has the effect of the law, though. So for all intent and purposes, it is the law.

Policy and guidance are just that. They're not the law, they're not regulations. If you see anything from a regulatory agency that is not verbatim from the law or regulation, it is a good chance that it is a policy or guidance. The talk today by Dorothy and me are really policy and guidance. We are presenting FDA's current thinking. They're not legally binding to the agency. They're not legally binding to anyone. Again, all it is just our current thinking.

If we say we don't have, in a policy, a concern for something, that doesn't make it legal. It still might be illegal, but we're just kind of portraying what our interests are, where our priorities are.

Case law are those situations where there's a disagreement between the regulatory agency, the FDA, and those whom we regulate. They'll go to court, the judicial branch, who will determine whether the agency has a correct interpretation of the law or indeed whether the law is even constitutional. And those decisions are in themselves have some impact and those are called case law.

Slide 24 (Legal Animal Drugs)

So, on the animal side, the only legal animal drug products are these four things. And that's it. They're approved new animal drugs, approved generic drugs or abbreviated new animal drug applications [ANADA]. Conditionally approved new animal drugs, as Dorothy had talked about. And she also talked about indexed drugs. Those are the only drugs that can be legally used in animals.

Slide 25 (Legal Human Drugs)

In addition, we do have legal human drugs. You can use those also legally, but we'll talk about that in a second. But legal human drugs on the human side are approved new drugs [NDA], approved generic new drugs [ANDA], and OTC, or over-the-counter, Drug Monograph products. Those are the products that you will typically see in a CVS or some type of drugstore on the shelves, over the counter for people to purchase and use. So aspirin, other topicals, things that the layperson can diagnose and utilize on their own. They are not approved, though, but they are legal.

Slide 26 (Unapproved Animal Drugs)

Unapproved animal drugs, and there are a number of them out there. We could go over historically why that is, but we are aware of and over the years there have been examples. But a lot of injectable products too that you may not realize, epinephrine, Lidocaine, atropine, some of the injectable calcium products for milk fever in cows. They're commercially available, but they're not legal. They have not undergone FDA approval. And again, I don't think we have time to go why that is and what, if anything, should be done about it, but at least they are registered. Those manufacturers are registered with the FDA and they undergo periodic inspection to make sure that they are manufacturing to Good Manufacturing Practices but they have not undergone the FDA's legal review process. We don't know about the safety and efficacy of any specific product. Whether that product really works because no one has looked at it.

Slide 26 (Unapproved Animal Drugs)

No preapproval review, no post approval monitoring. We don't know about the sales. We don't get adverse drug event reports. All the things you get with an approved product, a legal product, you don't get with the unapproved product. A lot of it we don't know about. Just their presence on the marketplace by default really is a disincentive for anyone to get a legal product on there. So depending on what it is, they may unfairly compete with approved or legal products. Also reduces the availability of any products in the future, whether that be indexed or conditionally approved. So the more that they're

utilized, the less that you have in your hands a drug that you know that the FDA has looked at, the safety, efficacy, has evaluated the ability of that firm to make a good quality product.

Slide 28 (Compounded Animal Drugs)

Compounded animal drugs. So compounding, which is kind of different from the human side. You've heard recently Congress enacted some laws in the past, and recently regarding compounding of human drugs, but none of those laws applied to the animal side. They're strictly for human drugs. It's pretty clear on our side the law and the law is this: If you compound, which is typically under a pharmacist, not like the unapproved drugs that just have wide scale marketing and distribution, but if it is a vet-driven prescription to a pharmacist to make something that is needed right then and there, a veterinarian can do that. The pharmacist can do that legally. The veterinarian can use that legally if, and only if, the starting material is an approved drug. An approved animal drug or approved human drug. So it may be legal, but you have to start with that.

If you're compounding from a bulk drug, just a raw ingredient, not from an approved drug, it will automatically be considered an unapproved new animal drug. It's not legal. Whether it's USP ingredient, whether it's pharmaceutical-grade, not pharmaceutical-grade, it doesn't matter in our context. It's just a bulk ingredient. And I just want to remind you too, USP pharmaceutical-grade is just a standard. It doesn't mean anything about safety or efficacy. All it is is a standard of quality of that chemical or substance. But it's an affirmation. So a firm will represent an ingredient as being USP or pharmaceutical-grade, but it's only through the FDA inspection approval process that it's determined whether it is or is not. USP is not a regulatory agency.

We have zero tolerance for compounding from bulk ingredients for food-producing animals. So that would go for any animal that -- well, in the case of research rabbits we'll talk about later, but in general, especially an animal intended for food, we have a zero tolerance for compounding.

Slide 29 (Compounded Animal Drugs)

Similar to unapproved drugs, there's no known quality of control manufacturing standards. State's oversight of pharmacies is not certainly to the extent of FDA's inspections. Sometimes they're more paper evaluations, document evaluations. So with a compounded product, you are not getting any known quality product or known manufacturing standard. So unknown assurance of purity, potency or stability. You don't know if an animal is not getting better, was it the incorrect diagnosis or was it a sub-potent product.

As a result, you can have potential animal safety and efficacy issues, unknown or unsafe residues if you're using a food animal. And it's very difficult for us to monitor. Unlike the unapproved drugs, which are registered with the FDA and we do inspect on a regular basis, these compounding pharmacies are not registered with us and they have no

reporting requirements and we just really don't even know where they are, much less are able to go out there and inspect them.

Slide 30 (Extralabel Drug Use)

The extralabel drug use regulation came out of an act or a statute passed by Congress and it's codified in the Code of Federal Regulations. And it involves the use of an approved drug in a manner not in accordance with the label. So if you're using an approved product in a different indication, species, dosage level, frequency, route of administration, if you're using it in any different way than what it was approved for, that's an extralabel use. But this law allowed veterinarians to do that legally, to prescribe them legally, if they're using approved, only approved animal drugs and approved human drugs.

Slide 31 (Extralabel Drug Use)

Few things, I think it's important to stress, and this is a quote, "Such use is limited to treatment modalities when the health of an animal is threatened or suffering or death may result from failure to treat."

Slide 32 (Extralabel Drug Use (Final Reg))

And when we published that final regulation, we said in the preamble to that in the Federal Register notice that phrase, "when the health of the animal is threatened," we mean that to include the concept of minimizing animal pain and suffering. And sometimes that might be through euthanasia. We put forth that's an interpretation, that's an acceptable extralabel use.

Slide 33 (Extralabel Drug Use)

It can only be veterinarian driven. So it has to be by, or on, the order of a veterinarian within a valid veterinarian-client-patient relationship. It should not result in violative residues and that's not just in meat, milk and eggs. We need to be careful and make sure those animals do not go into the animal food system. And that's going to a renderer. So if these drugs again are being used in an extralabel manner, it's important for the veterinarian to ensure that those residues don't go into animal feed, that those animals don't go into rendering.

Must be in conformance with all the other parts of the regulation. That goes without saying, although I just said it. And there are certain drugs listed in that regulation, I'm not listing them here or describing them here, but that list of drugs that are in that regulation, they cannot be used in an extralabel manner. They're prohibited from that.

Slides 34-44 (Extralabel Drug Use)

So let's go through. What can a veterinarian use legally in an extralabel manner?

- Approved animal drugs [Rx or OTC]: yes.
- Approved human drugs: yes.
- Conditionally approved: No. Dr. Bailey had said no. You cannot use them extralabelly.

- Indexed animal drug: No.
- Medicated feeds: No. Extralabel use cannot extend to drugs that are being administered to animals through feed.
- VFD drugs [veterinary feed directive]: those are basically medicated feeds with a quasi-prescription status, but no, because they're medicated feeds.
- OTC monographed drugs on the human side: No, because they're legal, but not approved.
- Unapproved animal drugs: No, because they're not approved.
- Drugs compounded from approved drugs: Yes, we get a check mark, so again a veterinarian can legally compound from approved drugs or have a direct pharmacist to do that.
- And then last, drugs compounded from bulk drugs: whether pharmaceutical-grade, USP, it doesn't matter, if the starting ingredient is a bulk drug from the legal standpoint, it's not a legal product.

Slide 45 (CPG Sec. 650.100 Animal Drugs for Euthanasia)

So let's touch into euthanasia. There's a policy online, a compliance policy guide and there's the number if you care to see it. And this is from that guidance. And again, remember, this is guidance, not a regulation. Euthanasia, painless killing, is widely practiced by vets to destroy unwanted pets and other animals -- all other animals, any animal. It's accomplished by a variety of methods. Pest control, though, that's one exception. If it's for the purpose of killing pests that's not considered euthanasia, at least by us, and that would be regulated by the Environmental Protection Agency.

Slide 46 (CPG Sec. 650.100 Animal Drugs for Euthanasia)

We consider euthanasia to be a drug, that sort of action results in a drug because they're clearly intended to affect the function of the body, namely by inducing death. But with one exception, I'll just talk about that, it's not really an exception, it's just another one of those unapproved drug categories, which is Pentobarbital. We consider all products to be new animal drugs and can only be legally marketed with an approval. Whether indexing can fit that, the MUMS people can talk about that, but it has to be at least a legally marketed product. The data must establish that the product results in humane and painless death.

Slide 47 (Animal Drugs Approved for Euthanasia)

These are the examples of the drugs that are actually approved by the FDA for euthanasia in animals.

Slide 48 (Animal Drugs Approved for Euthanasia)

The next slide shows those that are marketed. Those three products in black, those are the only ones that are presently being marketed, all of the Pentobarbital Phenytoin combinations, all are labeled for dogs.

Slide 49 (Animal Drugs Unapproved for Euthanasia)

And if you recall, there are unapproved drugs out there and this is one of those odd ones

out there, and that's another -- this is just a single ingredient, Pentobarbital. I know a lot of people use these products, but you might not have been aware that they're unapproved, not legal products. But again, they're out there, even our guidance acknowledges them, so that would be an enforcement discretion type of a situation.

Slide 50 (Medical Gases)

Just to round it off, medical gases are used for euthanasia purposes. They're not approved, but they are certified. So when they're certified, that means for these uses. And I'm not going to go through them all, but these gases are certified or can be used legally in animals for these various purposes. Any other purpose would not be a legal use.

Slide 51 (Enforcement Discretion)

So let's end with the main thing, because a lot of this seems there's not much to use legally in a research situation. And that very well may be true. There is enforcement discretion. The agency has a lot of issues on the animal side, everywhere else, but we need to really protect public health as much as possible. Human public health, making sure that the food they consume does not have drug residues in it, that target animals, especially for the major species, but we care about all, that they're safe and effective. That humans administering them aren't harmed by them. But the law we have is similar to the law for the humans, but they have one species. We have very many species used in different ways. So we use enforcement discretion which doesn't mean that if we're not taking action it makes that product legal, it's just that we're trying to be reasonable. We do not seek to disrupt basic research. We do not seek to disrupt the care of animals in a research setting.

I think it's important for you to know what's legal from our standpoint, but when it comes down to it, you're not going to see us in research settings taking actions. It's more for wide scale, people selling those drugs, abuses of the situation. However, we do really feel strongly that the indexing process exists to help the research people because it's always good even in a research setting to have a drug that you know is behaving in a certain way, that isn't causing issues that might be adversely affecting the research protocol itself.

So again, a lot of it is enforcement discretion. It doesn't mean we're totally fine with it. It doesn't mean certainly that it's legal, but it is an indication and again, our interest is not to disrupt animal research. And you'll hear the approach in the research setting next, and that's fine. Again, we acknowledge that and support that. Thank you.

Slide 52 (OLAW)

>> Wolff: Thank you, Dr. Bataller. I will now give OLAW's perspective. OLAW has incorporated FDA's regulatory language into our new definition of a pharmaceutical-grade substance. Let me read the new definition to you. A pharmaceutical-grade substance is any active or inactive drug, biologic, reagent, etc., manufactured under Good Manufacturing Practices, which is approved, conditionally approved, or indexed by

the FDA or for which a chemical purity standard has been written or established by a recognized compendia, such as the US Pharmacopeia-National Formulary and the British Pharmacopeia. Substances that do not meet these criteria are non-pharmaceutical-grade.

Slide 53 (OLAW)

OLAW has extensive guidance in [Frequently Asked Question F4](#) on our website. Here's a summary of that guidance. OLAW and USDA agree that pharmaceutical-grade substances, when available, must be used to avoid toxicity or side effects that may threaten the health and welfare of vertebrate animals and / or interfere with the interpretation of research results. It is frequently necessary to use investigational substances, veterinarian or pharmacy compounded drugs, and / or Schedule I controlled substances to meet scientific and research goals. The IACUC is responsible for evaluating the potential adverse consequences of such substances when used for research.

FAQ F4 goes on to say that cost savings alone are not an adequate justification for the use of non-pharmaceutical-grade substances in animals. We have added some new language to FAQ F4 which states unavailability or shortages of pharmaceutical-grade substances may lead to cost increases. The IACUC may determine that this justifies the use of a non-pharmaceutical-grade substitution. You will find that this language is very similar to the language used by USDA in Policy 3. The remainder of the guidance in F4 is unchanged and you can read that on the OLAW website.

Slide 38 (*Guide for the Care and Use of Laboratory Animals*)

The PHS Policy requires institutions to base their programs of animal care and use on the *Guide*. The *Guide* says that pharmaceutical-grade substances should be used when available. The use of non-pharmaceutical-grade substances should be described and justified in the animal use protocol and be approved by the IACUC. For example, when necessary to meet the scientific goals of a project or when pharmaceutical-grade product is unavailable. In such instances, consideration should be given to the grade, purity, sterility, pH, pyrogenicity, osmolality, stability, site and route of administration, formulation, compatibility, and pharmacokinetics of the chemical or substance to be administered, as well as animal welfare and scientific issues relating to its use.

Dr. Clarke, would you like to give the perspective from the USDA's side?

Slide 56 (Policy 3 – Veterinary Care)

>> Clarke: Yes. As far as the USDA, Policy 3, Veterinary Care: pharmaceutical-grade substances are expected to be used in USDA-regulated species when available, even in acute procedures. This includes, but is not limited to compounds, medications, drugs, vehicles, and diluents.

APHIS recognizes that some substances are only available as non-pharmaceutical-grade. These are test articles, novel compounds, and those from compounding. IACUC approval is required for the use of a non-pharmaceutical-grade substance. Cost savings alone is

not sufficient justification. Approval may be given if shortage or unavailability of a pharmaceutical-grade substance has resulted in cost increases. Thank you.

>> Wolff: Thank you Dr. Clarke, now for the AAALAC perspective, Dr. Bradfield?

Slide 57 (AAALAC FAQ)

>> Bradfield: Thanks, Axel. Hi, everyone. John Bradfield here with AAALAC International. We have a [Frequently Asked Question](#) on our website and you will find that on the reference list in the end of this webinar. But our FAQ also acknowledges that there are a number of instances where non-pharmaceutical-grade substances, preparations, are used in research animals. We also have sort of similar language that OLAW just described and our definition for sake of clarity of a pharmaceutical-grade compound is one that's defined as any active or inactive drug, biologic or reagent, for which a chemical purity standard has been established and recognized by a national or regional pharmacopeia.

In short, the AAALAC FAQ describes whenever non-pharmaceutical-grade drugs are used that they be approved by the animal care and use committee. The Council on Accreditation made two distinctions about the use of non-pharmaceutical-grade drugs, clinical use and research use.

So for clinical use, drugs or preparations that are used to treat animals, and the Council also included things like analgesics and anesthetics in this definition. These are compounds to maintain the health of the animal. That whenever possible pharmaceutical-grade drugs must be used for the clinical use in animals. And the Council used that term 'must' very intentionally.

The other side of the coin is research use. These are compounds used to accomplish the scientific aims of the study. Many times these are non-pharmaceutical-grade according to the definition, such as it is. So in these cases the Council has stated that pharmaceutical-grade is preferred, but when non-pharmaceutical-grade is used or required that there be a scientific justification described for that and considered by the animal care and use committee with additional consideration of attributes of the preparation such as purity, grade, stability, pH, osmolality, etc.

So in short, that's the AAALAC FAQ. Bottom line being that when non-pharmaceutical-grade compounds are used that they're approved by the IACUC. Thanks.

>> Silk: Thank you, John.

Slide 58 (Case Study)

Now we have a case study, which will provide an opportunity for our speakers to provide their unique perspective on a situation that an IACUC might encounter. May a PI use a commercial euthanasia solution at 50 milligrams per kilogram, a dose less than

recommended for euthanasia, for a terminal procedure in rabbits or must he use a pharmaceutical-grade anesthetic formulation of sodium pentobarbital?

So now we're going to put some conditions on this situation. As part of IACUC approved research, the rabbits undergo a terminal Langendorff procedure during which the rabbit is under deep anesthesia and a cardieotomy, removal of the heart, is performed. Once the animal is under deep anesthesia, the procedure is completed in less than a minute. No other procedures are performed until after the heart is removed and the animal is dead. No other anesthetic euthanasia agent is acceptable as it will compromise cardiac physiology needed for the studies that will be conducted on the myocardium after the heart is removed.

So now we come to the actual question. Does this fall into the category of either a terminal surgery? That is, where euthanasia solution is not permitted? Or is this a two-step euthanasia process in which a euthanasia solution may be used, but at a lower dose since the adjunctive cardieotomy confirms death?

Slide 59 (OLAW and USDA Position)

>>*Wolff*: OLAW and USDA have agreed on the following response to this scenario:
Euthanasia solution is only to be used during humane termination of an animal's life.
Any other use is contrary to the label instructions and considered extralabel use. OLAW and USDA have stated that euthanasia solution is not to be used as an anesthetic for survival or non-survival procedures.

OLAW and USDA have stated that a euthanasia procedure may be performed in which an animal is given euthanasia solution after which an irreversible procedure such as a terminal perfusion, exsanguination, or tissue harvest is immediately conducted to ensure death. Under these circumstances the euthanasia solution is being used as intended with the final outcome being death. Any delay, however, in the terminal steps to conduct other potentially painful procedures would change the euthanasia to non-survival surgery and be an unacceptable use of the euthanasia solution.

Carol, did you have any additional comments on this?

>>*Clarke*: No. USDA concurs with everything you said.

>>*Wolff*: John, AAALAC perspective on this?

>>*Bradfield*: I think the AAALAC perspective; you have touched on the issues that would be germane for the IACUC to consider when considering a protocol describing this kind of a procedure. We would expect that the IACUC provide sound judgment and rationale for considering animal well-being in the scientific aims of the study.

I think there would likely be some potential real concern about the use of a euthanasia agent for a survival procedure. It's hard to imagine a scenario in which that would be justified or appropriate. But for a non-survival procedure, we would expect the IACUC to think about the animal well-being, the timing of administration of the agent versus removal of the tissue, all those things that you mentioned that are critical, we would expect the IACUC to consider those when making its judgment on approval or not.

>>*Silk*: Dorothy or Neal, would you like to comment? No comments.

Slide 60 (Question 1)

>>*Babcock*: Okay. This is a question that came in before the webinar. The use of saturated KCl is an acceptable method of euthanasia according to the AVMA Panel on Euthanasia. A pharmaceutical-grade saturated KCL preparation is not commercially available. What is the position of each of the organizations speaking today on the use of KCl from a chemical supply company for euthanasia while the animal is under a general plane of anesthesia? Would our panelists please comment on that?

>>*Bataller*: Well, again, just from the FDA's standpoint, unless it's an approved product, it would be an illegal product or not a lawful product. So I think that's all we would have to comment on that. Whether the bulk drugs, pharmaceutical-grade or not, again, it's just using a bulk to create a drug would be the position that it's just not legal.

>>*Wolff*: If a pharmaceutical-grade version of KCl and the formulation needed for the study is not available commercially, then that would be an acceptable scientific justification for the IACUC to consider in approving the use of a chemical grade preparation. If this is a common method within the animal program, an institution-wide policy could be developed as a standard operating procedure. This SOP could be referenced by the PI in the protocol. The SOP must include clear guidelines on reconstitution, handling and storage.

>>*Babcock*: Carol, would you like to comment on this?

>>*Clarke*: The USDA agrees with the OLAW statement.

>>*Babcock*: John, how about AAALAC?

>>*Bradfield*: I would refer back to the AAALAC FAQ for the important parts I think in my reply. First of all the AVMA Panel on Euthanasia [AVMA Guidelines for the Euthanasia of Animals] is a resource that the Council on Accreditation has adopted as a valuable resource for IACUCs to consider when determining methods of euthanasia and their appropriateness for each case-by-case scenario. So the AVMA Panel we consider an important reference resource. I guess that's the first point. The second is that this kind of decision is well within the purview of the IACUC to make a judgment about whether or

not the use of the agent is -- there's a rationale and a justification for it, and then making a judgment about the acceptability of its use in a case-by-case basis. So we would leave this in the hands of the IACUC to make that judgment. Thanks.

Slide 61 (Question 2)

>>*Babcock*: Okay. We have another question. Dr. Bataller listed six FDA approved products with pentobarbital as the active ingredient, only three of these which are currently available. How do these products difficult from Fatal-Plus, which is a commercial product, but not FDA approved? Dr. Bataller?

>>*Bataller*: Well, as you can imagine my response will be that three of them are legal and the Fatal-Plus is not legal. That's a simple answer. The three approved ones have -- they were examined as far as working, being at least effective. They were examined as far as the manufacturer really being able to make what it says it could make. The Fatal-Plus does not have that. The Fatal-Plus we know nothing about post-market too. Having said that, the Fatal-Plus, the manufacturer and the others of the single pentobarbital are inspected by the FDA periodically and they are assessed for good manufacturing practices.

So the quality presumably of the approved one is better, but other than the legal standpoint, one being approved, the other not, I would imagine those other differences, if any, would be detected by the user. But at least they're inspected to some extent by the FDA.

Slide 62 (Summary)

>>*Silk*: Okay. Well, thank you. We've heard a lot of complex information today, so we've made a summary of the take-home messages that we think will be useful to your IACUC.

- FDA regulations and guidance focus on safety and efficacy of commercial animal and human drug products.
- OLAW, USDA, and AAALAC focus on research animal welfare.
- Guidance by FDA, OLAW, USDA, and AAALAC overlap during both clinical and research use in lab animals.
- Legal choices provide the least risk but may not be appropriate or available in all cases.
- Use of non-pharmaceutical-grade substances should be described and justified in the animal use protocol and be approved by the IACUC. Cost savings alone is not sufficient justification.

I'm sure that all of you out there have questions, so if you email them to us, we and all of the presenters will work together to provide answers, which we will post on the OLAW website.

Slide 63 (References)

>>*Babcock*: On this next slide FDA has provided links to resources you may find useful. You can download a PDF copy of the slides or the transcript of this webinar from the OLAW website.

- *Animaldrugs@FDA.gov*
<http://www.accessdata.fda.gov/scripts/animaldrugsatfda/>
- *FOI Summaries for Approved Drugs*
<http://www.fda.gov/AnimalVeterinary/Products/ApprovedAnimalDrugsProducts/FOIADrugSummaries/ucm056898.htm>
- *MUMS*
<http://www.fda.gov/AnimalVeterinary/DevelopmentApprovalProcess/MinorUseMinorSpecies/ucm070206.htm>
- *Indexing*
<http://www.fda.gov/AnimalVeterinary/DevelopmentApprovalProcess/MinorUseMinorSpecies/ucm125452.htm>
- *Unapproved Drugs*
<http://www.fda.gov/AnimalVeterinary/GuidanceComplianceEnforcement/ComplianceEnforcement/UnapprovedAnimalDrugs/default.htm>

Slide 64 (References)

The next slide has more references for you.

- *OLAW FAQ* http://grants.nih.gov/grants/olaw/faqs.htm#useandmgmt_4
- *USDA Policy 3*
http://www.aphis.usda.gov/animal_welfare/downloads/Animal%20Care%20Policy%20Manual.pdf
- *AAALAC FAQ C. 9.* http://aaalac.org/accreditation/faq_landing.cfm#B9
- *ILAR Guide, 8th edition, 2011, page 31*
http://www.nap.edu/openbook.php?record_id=12910

Slide 65 (OLAW Online Seminar)

I would like to thank Dorothy and Neal for the terrific explanation of the FDA policies on veterinary pharmaceuticals. I'd like to thank Carol and John for providing USDA and AAALAC perspective. And to all of you for participating. The next OLAW seminar is on September 24th, 2015. We haven't selected a topic yet, but we will let you know through the usual channels of communication. Thank you and good-bye.

Additional Submitted Questions Not Addressed During the Webinar

[Pending]

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