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FDA's New Guidance on Compounding Bulk Drug Substances
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Slide 1: FDA's New Guidance on Compounding Bulk Drug Substances
>> *Cate Pritchard*: Good afternoon. I am Cate Pritchard, part of the NIH Office of Laboratory Animal Welfare. Today is Thursday, September 8th, 2022, and I'm pleased to welcome you and our speakers to our webinar today, titled "FDA's New Guidance on Compounding Bulk Drug Substances."

All right, let's get started with introductions for our speakers. Dorothy Bailey, DVM, is a Veterinary Medical Officer in the Office of Minor Use and Minor Species Animal Drug Development at the US FDA Center for Veterinary Medicine. She has been with the FDA for 16 years and is the head of the indexing program. Dr. Bailey graduated from the Virginia-Maryland College of Veterinary Medicine in 2003.

Amber McCoig, DVM, MPH, is a Senior Veterinary Medical Officer, Science Policy, in the Office of the Director at the US FDA Center for Veterinary Medicine. She has been with the FDA for 14 years, including serving as the Deputy Director for CVM's Division of Compliance. She's a 2005 graduate of the University of Missouri College of Veterinary Medicine, and she's also an adjunct professor in the University of Missouri Department of Public Health and teaches veterinary public health policy.

And lastly, but certainly not least, we have Nicolette Petervary, VMD, MS, DACAW, representing OLAW today. Dr. Petervary is the Director of the Division of Policy and Education here at OLAW. She received her veterinary degree from the University of Pennsylvania, her master's in Comparative Biomedical Sciences from North Carolina State University, and is a diplomate of the American College of Animal Welfare. Her past experiences include private clinical practice in small and exotic animal medicine, research, and regulatory veterinary medicine. And with that, I'll hand the presentation over to Dorothy.

Slide 2: FDA Guidance on Compounding Bulk Drug Substances: Guidance for Industry #256
>> *Dr. Dorothy Bailey:* Thank you to Cate, for the introduction. I was also thanking OLAW for inviting Amber and I to come to speak with you all today. As Cate said, we are going to discuss the FDA guidance on Compounding Bulk Drug Substances for Office Stock or Guidance for Industry Number 256.

Slide 3: Today's Presentation
Here we go. First, I'm just going to give you an overview of the presentation. The first part: we're going to cover the three legal marketing statuses for animal drugs and some information on pharmaceutical grade substances. And then the second part: Amber is going to present some information related to drug compounding and GFI 256.

Slide 4: Learning Objectives
So, the topics that I'm going to present, specifically: I'm going to cover the three legal marketing statuses for animal drugs, which are Approval, Conditional Approval, and Indexed; I'm going to tell you ways to identify these drug products; and then I'm actually going to hand it over to Nicolette and she's going to present a few slides on pharmaceutical grade substances.

Slide 5: Definitions
A few definitions that will be helpful to you all during this presentation are here. First, the FDA considers *major species* to be horses, dogs, cats, cattle, pigs, chickens, and turkeys, and then essentially everything else is considered *minor* except for humans. A *minor use* means drugs intended for use in a major species for disease that occurs infrequently, or in limited geographic areas and only a small number of animals annually.

Slide 6: Important Note
One very important note is when I'm discussing the legal marketing statuses for animal drugs and our regulation of their use, I'm talking about when you use these drugs for the *clinical care* of animals— so not when the drug is the subject of the research.

Slide 7: What is the difference between FDA-Approved, conditionally approved, and indexed drugs?
Now, what is the difference between FDA-approved, conditionally approved, and indexed drugs?

Slide 8: Approved Drugs
FDA-approved drugs have had adequate and well-controlled studies conducted to demonstrate substantial evidence that the drug is safe and effective for its intended use. Environmental safety, user safety, and human food safety (if the drug is for use in a food-producing animal), have also been addressed, and manufacturing studies have been conducted to ensure the strength and purity of the drug.

Slide 9: Approved Drugs (continued)
All of the data is reviewed by FDA scientists, and once the drug is approved, it is manufactured in accordance with current Good Manufacturing Practices, or GMPs. This is to ensure quality and consistency of the drug product. Extra-label use is legal for approved drugs under certain circumstances.

Slide 10: Visit the FDA site to read the ins and outs of extra-label drug use in animals, including:
On this slide, we've provided you with a link at the bottom that will take you to an FDA web page that will explain extra-label use for veterinarians. The bullets here represent some of the information that is included on that web page.

Slide 11: How to Recognize Approved Drugs

So, ways to recognize an approved drug. The label *may* have, and I do mean *may*— some of the older approvals may not have this information on the drug— but they may have a six-digit application number. This can either be a new animal drug application (or NADA) number, or for generic drugs, it would be an abbreviated new animal drug application number (or an ANADA number). The label may also include a statement that says, "Approved by FDA." I've included a couple of examples here that will show you how this information might be represented on labeling. If you do not see either the application numbers or a statement that says approved by FDA on the labeling, we do have a searchable database of all approved drugs on the FDA website. It's called Animal Drugs @ FDA, so you could go there to search for the drug. We've included a link on this slide.

Slide 12: Conditional Approval

So, now we're going to move on to conditional approvals. For conditional approval, all approval requirements have been met except for effectiveness, but the FDA has determined that there is a reasonable expectation that the drug will be effective. Once it's conditionally approved, the drug can be marketed for up to five years while the drug sponsor completes the effectiveness technical section. Once that section is complete, then the drug would be considered fully approved. Conditional approval is an incentive for minor uses in major species or for drugs for use in minor species. The FDA has recently expanded conditional approval to also include drugs that treat a serious or life-threatening condition, or drugs that meet an unmet animal or human health need. But in addition to those two things, demonstrating effectiveness also needs to require complex studies— you know, complex or difficult studies— to qualify. For conditionally approved drugs, extra-label use is prohibited for these products.

Slide 13: How to Recognize Conditionally Approved Drugs

The labeling for a conditionally approved drug will include a six-digit application number, and it will also include language stating that it's pending full approval by the FDA. We provided an example here, and this is what it should look like if you see it on the labeling.

Slide 14: Indexed Drugs

Alright, so now we're going to move over to indexing. Indexing is an alternative to the approval process, and it provides a legal marketing status— so the drug is considered unapproved but legally marketed. The target animal safety and effectiveness for an indexed drug is determined by a risk-benefit analysis that is conducted by an outside expert panel. This expert panel *does* have to be accepted by the FDA to do this review, and the FDA reviews the report from the expert panel of their risk-benefit analysis. We also review a summary of the manufacturing process— so we do not see study data related to manufacturing like you would for an approval, but we do review a summary of the process. Then we also look at information to address user and environmental safety. Before we put the drug on the index, the drug holder, which is the manufacturer of the product, signs a commitment to manufacture the product in accordance with good manufacturing practices. Indexing is available only for drugs for use in non-food minor species. The legal standard is actually that we have to have a reasonable certainty that the animal will not be consumed by humans or food-producing animals after receiving the index product. And lastly, extra-label use is prohibited for indexed drugs.

Slide 15: How to Recognize Indexed Drugs
The labeling for an indexed product will include a six-digit minor species index file or a MIF number. This number always starts with a nine, and then it also is going to include certain statements that are required for indexed drugs regarding legal marketing status. I've actually provided you two examples here, because sometimes those statements regarding legal marketing status can look different depending on the size of the label. The full statement is the example at the top of the slide that starts with legal status, and then that example up underneath that— you can see where if it's a small label like a vial label where we cannot *fit* the entire statement, we will allow them just to put a legally marketed with the MIF number and the extra-label use prohibition statement. We also have the list of the indexed drugs on our website, and it includes all the drugs that are indexed and there's also links to the freedom of information summary and the labeling for these products.

Slide 16: Are There Any Similarities Between FDA-Approved, Conditionally Approved, and Indexed Drugs?
So, we've talked about the difference between the different legal marketing statuses, but are there any similarities?

Slide 17: Similarities Between the Legal Marketing Statuses
Yes, there are. All of these drugs go through a pre-market process that includes FDA review of information related to safety, effectiveness, and manufacturing, and all are monitored once they're marketed.

- For approved drugs, that monitoring includes inspection of the manufacturing facilities. They submit annual reports related to the quantity that is marketed each year, and then FDA also reviews promotion and advertising materials.

- For conditional approval, there's an annual renewal process where each year they have to tell the FDA what progress they've made toward completing their effectiveness technical section, and once they do complete that effectiveness technical section, the product becomes fully approved. Then it's marketed and monitored just like any other approved drug would be.

- For indexed drugs, the manufacturing facilities for indexed drugs are eligible for inspection by the FDA. They do submit annual reports to us that includes information related to the quantity marketed and any minor changes to the labeling or to the manufacturing process. We also review promotion and advertising materials for those products as well.

A very important similarity between all these products is that you, the end users, can report adverse drug events for any of these products; we've provided a link to a webpage that will tell you how to do that.

Slide 18: Pharmaceutical Grade vs Indexed Drugs
And now I'm actually going to let Nicolette take over and discuss pharmaceutical grade substances.

>>Nicolette Petervary: Thanks, Dorothy. So, as you've heard from Dr. Bailey: you've heard the terms *approved, conditionally approved,* and *indexed* drugs. You have not heard the term *pharmaceutical grade*. So, my job here is to explain what *pharmaceutical grade* is. And firstly, it's not an FDA term. It is a term that OLAW uses describing any active or inactive drug, or biologic, or similar, manufactured under good manufacturing practices. It can include approved, conditionally approved, and indexed drugs.

Slide 19: Pharmaceutical Grade vs Indexed Drugs (continued)
Why is this? It's because all of these drugs go through an FDA process that involves review of information relating to safety, effectiveness and manufacturing. So, this is the reason these are considered under the umbrella of pharmaceutical grade. But this is not an FDA term.

Slide 20: Pharmaceutical Grade vs Indexed Drugs (continued)
Another thing that is important to remember is that even when using what we consider to be pharmaceutical grade substances, you are to adhere to FDA requirements where applicable. There should always be attention to appropriate reconstitution, labeling, compounding, use, and storage. And with that, I would like to introduce Dr. McCoig to talk about the second portion of the FDA presentation.

Slide 21: Guidance for Industry #256: Compounding Animal Drugs from Bulk Drug Substances
>> Amber McCoig: All right. Thank you. I really appreciate this opportunity to speak with you, and I'm going to continue on with the presentation and dive a little bit deeper into our Guidance for Industry 256. This came out in April, and it discussed compounding animal drugs from bulk drug substances. So today I'm going to talk about the difference—just kind of go over again— *approved* versus *unapproved*; talk about compounding under the Animal Drug Use Clarification Act; and discuss compounding for bulk drug substances.

Slide 22: Legally Marketed New Animal Drugs
So, here's just a quick overview. There's a difference between *approved* and *unapproved marketed;* and so, for us, an *FDA-approved* drug is going to be something that has gone through pre-market review as well as post-market oversight— so we have things that we monitor after the drug is in the marketplace, such as their manufacturing, their labeling, and things like that. I know that Dr. Bailey already went over the *conditionally approved* and also the *indexed*, so I don't need to bother you guys with covering that again.

Slide 23: New Animal Drug Approvals
So, for us, these new animal drug approvals— they show that we've had data that demonstrates that they're safe, effective, that they have manufacturing quality, and adequate labeling. And again, FDA monitors adverse events as well as product defects, advertising, and changes in manufacturing and labeling. So, these are things that you do not see in compounded products or in unapproved drugs.

Slide 24: Why vets need to compound animal drugs
We recognize that veterinarians do need the ability to compound animal products and animal drugs. We know that this is a challenge that we face daily. Before 1994, as many of you know, we did not have the ability to do that, and Congress passed the Animal Medicinal Drug Use Clarification Act at that time. This allowed veterinarians with a valid veterinarian client-patient relationship to legally prescribe approved human or animal drugs for extra-label use. This included compounding from approved products.

Slide 25: Animal Drug Compounding
When you are compounding an animal drug, that's anything that involves the process of combining, mixing, or altering an ingredient to create a medication that is tailored for the needs of an individual animal or a small group of animals. So, I want to just stress the individual or small group of animals. I think for this audience, that's probably an important point to make sure to point out. Animal drug compounding falls into two different categories. We have the approved drug compounding, which as I said earlier, is legal extra-label use under AMDUCA, and then we have compounding from bulk drug substances. So, this creates an unapproved new animal drug under the Federal Food, Drug, and Cosmetic Act. That means that when you are compounding, and not using the approved product, that is technically an illegal product.

And I think that some of the common misconceptions that we have are that compounded drugs are generic drugs, or compounded drugs have somehow been evaluated by FDA. And they have not. The bulk drug substance has not been reviewed as part of an application. So, unless they are using an approved drug, and then mixing that and coming up with a new product, with the base being the approved product, then they're making an unapproved new animal drug, and that is with the bulk drug substances.

Slide 26: What is the difference?
So, it is possible you could have two different bottles of medication that have the same active ingredient, and they're going to appear very similar. And sometimes it's difficult to even recognize that you have a compounded product. And I think as Dr. Bailey went through, there are some key things that you can look on the label to see if it's an FDA-approved product. But some of the other differences to note are just that compounded drugs do not have the pre-approval evaluation, so they have unproven safety, we don't know about their bioavailability, and we also don't know about their effectiveness, quality, or stability. And stability is going to be very important when we're talking about office stock or things that are kept on a shelf. They also, again, don't have the regulatory requirements to have that post-monitoring that we have with approved drugs, and that's going to include adverse events and product defects. So, FDA and the public may never be aware when these things come up.

Slide 27: Concerns with Animal Drug Compounding
And we do have safety concerns with animal drug compounding. We are specifically concerned with drugs that could present human or animal safety issues, so that could include the human handling of the drug itself. We also are, for the same reason, concerned about compounding for food-producing animals because that could then cause a residue that could get into the food supply. We're concerned about copies of approved, conditionally approved, and indexed or marketed drugs, because we think it's

important to protect our approval process. And we also, as I said earlier, have some increased concerns about office stock, and I'm going to go into that now.

Slide 28: Concerns with Animal Drug Compounding (continued)
So, drugs that present a particular animal safety concern would be drugs that contain more or less of the labeled amount of an active ingredient, or drugs that have a bacterial contamination or fungal contamination. We have seen some examples of this happening in the past. In 2009, compounded vitamin and mineral injectable solution had about 100 times the intended selenium and that led to the death of 21 polo ponies. In 2014, we had compounded toltrazuril and pyrimethamine oral suspension that had over 20 times the labeled pyrimethamine, and this led to two horses dying and the illness of six others. And in 2019, the same product, compounded toltrazuril and pyrimethamine in an oral paste contained 18 to 21 times the labeled pyrimethamine, and this crossed over into two states as well, and three horses died. It's also important to point out again that these are only the ones that we hear about. A lot of these things, *we* learn about them when they're in the news because they are not required to report these adverse events to us. FDA may not be aware. That also means that we wouldn't be able to take action to help mitigate anything that's happening. Additionally, we have had over 40 voluntary recalls of compounded animal drugs since 2016. All of these recalls were in response to public health concerns. That included lack of sterility, microbial contamination, failed stability, manufacturing issues, and unsanitary conditions.

So, drugs that are copies are a concern, as I mentioned, because they would compete with approved products. This could undermine the incentives for firms to investigate and get new drugs approved or indexed for animals— and as you all have probably experienced, it's already difficult to get approved products for many minor species. So, we feel that compounding could really have an impact on whether or not people are putting the resources into doing that.

And finally, we are especially concerned with the potential risk of harm from office stock. These products that are kept on a veterinarian's shelf, they're going to be in larger quantities, so they can be widely distributed to different veterinary hospitals or different patients. That means it could endanger a larger number of animals if they've been compounded improperly or under unsanitary conditions. And also, we don't know the stability of these products, so they may be ineffective after they sit on the shelf for too long.

Slide 29: Primary Objectives GFI #256
All that being said, we know that there's a legitimate veterinary medical need for compounding from bulk drug substances, and we want to preserve that ability. In this guidance, that's really what we aimed to do— to help veterinarians when they need access to compound animal drugs. We recognize that veterinarians need this access, and we know that there are specific patients that require it. So we want to just protect animals and humans from any safety issues that we can, and we want to preserve the integrity of the approval process, and that is what we put forward in this policy.

Slide 30: Guidance for Industry #256
The guidance describes our approach to these situations and outlines how we intend to exercise enforcement discretion or provide flexibilities for pharmacists and veterinarians who compound animal drugs from bulk drug substances. The policy addresses three different categories, and that includes:

- Individual patient-specific prescriptions
- Office stock for non-food-producing species
- Antidotes for food-producing animals or sedatives for free-ranging wildlife.

It's really important that these different categories are recognized because there has been some confusion about different things that apply to specific categories. I just want to make sure that everyone understands that the patient-specific prescriptions (which could be, again, an individual patient or a group of animals) do not have a bulk drug substance list, and we're going to kind of go into more details on what that means in a minute.

Slide 31: Changes from Draft to Final
So we did not simply finalize our draft guidance; if you had an opportunity to review the draft guidance that came out in 2019, we developed and implemented a rigorous process. We had over 2,200 comments that we reviewed, and based on all the feedback that we've received from veterinarians, people from the industry, and the public, we substantially modified things and made those changes. In the final guidance, we continue our policy that veterinarians are not limited to any list if they're compounding for a specific patient or a group.

We also do not intend to generally take enforcement action if they are compounding a copy but have a medical rationale to have the copy and cannot use the approved drug for that patient or group. We also have simplified our definition of a copy, so our definition of a copy is now something that has the same active ingredient and is given by the same route of administration. That may seem like a broad group, but that is going to help people to not have to determine whether or not what they're making is a copy. We want it to be simple so people know when a medical rationale is needed. And I'll go into more detail in a minute, but a medical rationale is *only* needed if you're making a copy of an approved product. If you're doing a patient-specific prescription that's not a copy, we do not ask for any type of medical rationale. And lastly, we also have asked in this guidance that compounders report ADEs to the FDA.

Slide 32: Changes from Draft to Final (Continued)
One of the things that we did: we streamlined our process for nominations of office stock. And in our food-producing animal category, we included free-ranging wildlife. So, I am going to go into more details on all of these things.

Slide 33: Nominations to the Lists of Bulk Drug Substances
We'll start with the nominations to the bulk drug substance lists.

Slide 34: Office Stock for Nonfood Animals, Antidotes for Food Animals, and Sedatives for Free-ranging Wildlife
We have three different lists that you can use for office stock or for food animals. Office stock is for non-food animals, and the list that's for food animals, which includes wildlife, can be for office stock or for

patient-specific prescriptions. It's required because you cannot compound products for food-producing animals, so we have to have a list to identify those bulk drug substances that can be used in any situation that they're needed in.

One of the things that is consistent on all three of those lists is that they can't be a copy of an approved product. Also, they can't have the same active ingredient as something that could be used in an extra-label manner. So that's consistent with AMDUCA. And we can't have any safety concerns about that particular bulk drug substance.

Slide 35: Office Stock for Nonfood Animals
So, we take nominations to all of these lists. We have a docket that is available and the nominations can be submitted there. We intend to include bulk drug substances on our office stock list if it's needed urgently to avoid animal suffering or death. So that could just be that, for some reason, the animal needs to be treated and there is not time to wait for a prescription to be filled.

Slide 36: Antidotes for Food Animals and Sedatives or Anesthetics for Free-Ranging Wildlife
Some of the additional circumstances that we have for food-producing animals and free-ranging wildlife is that it's an antidote for food animals or a sedative or anesthetic for free-ranging wildlife and that some scientific information is available to provide a withdrawal, withholding, or discard time, or a means to ensure that the animal does not enter the food supply.

Slide 37: What needs to be included in my nomination?
And, like I said, we have a docket and we accept nominations. Those nominations could come from veterinarians who need to use a product, also from pharmacists, and we ask that people use the docket so others can also participate and the onus is just not on one person to get all the information. We want this to be an open process where people can see what has been nominated, also so they don't have to duplicate efforts. When we are looking at nominations, we really look at how the product is going to be used, so we need to know the chemical name, the common name, and then a description, because we have many different products for humans and animals. So, we need to know the dosage form and the strength and concentration; for the dosage form, that that could also be a range, because we recognize that this may be for different species or different sizes of animals. Same thing with species to be treated, there can be more than one species included on a nomination. The disease or condition to be treated is asked for to aid us in our review of materials. It's hard for us to determine if there is a safety issue if we don't have the ability to look into why it's being used and specifically what species it's being used in. And then, also, why it's needed for urgent treatment.

Slide 38: What needs to be included in my nomination? (continued)
So again, the other "why" that we're talking about if there's no FDA-approved drugs to treat the disease/condition, we just ask that you provide a statement that says there's not an approved drug that can meet this need. If there is an approved drug, and it has the same active ingredient, we just need a couple of lines of why that approved drug cannot be used.

For all of this information, we only ask that you provide it if you know it. We recognize that sometimes the people who are prescribing may not have all the information, they may not know that it's a tablet

that has a specific coating. That's why we have a process where we can get back to you and ask questions, and we also have things on the docket so that pharmacies and others can also participate in adding to the docket and helping us to make those decisions.

Slide 39: What needs to be included in my nomination? (continued)
And then also, again, if known, the nomination should include if there are any human or animal safety concerns. If the drug's going to be used as an antidote for a food-producing animal or a sedative or anesthetic for free-ranging wildlife, we're asking if there's scientific evidence for a withdrawal time or any other information that can be provided.

Slide 40: How do I submit a nomination?
And I think I've said this several times, the nominations are submitted to our docket. One of the things that we changed from the draft to the final is we wanted to provide a way to have two-way lines of communication. We want to help people nominate things to our lists, so we're available and we have a compounding mailbox to assist if for some reason you're having trouble with the docket or having trouble understanding what information is needed. So, please feel free to use that mailbox. We're also going to use that so that we can reach back out if we have other questions. We don't want people to feel like they're submitting a nomination that goes into a black hole and we don't hear about it again.

Slide 41: How do I submit a nomination? (continued)
And I think that that is another important point. If something is nominated, and it goes into the docket, we do a brief look to just see if there are any major safety issues that we're aware of. Barring that, that nomination is immediately put on our list of drug substances that are currently under review.

So, just to make things very easy, we have five different lists for you to review…but when drugs go on the list of bulk drug substances that are currently under review, that means that they can be used during that time while they are on the list and we're going to provide enforcement discretion at that time. We thought that this was important so that when the guidance came out, that didn't mean that we were immediately pulling things while we were reviewing nominations. We don't have the ability to give a specific timeline for how long nominations will take, and we understand that could be stressful for people who are needing these drugs in order to treat their patients. So, we are providing discretion during this time, and it's going to remain on the list throughout the review of the nomination.

Slide 42: What happens after I submit my nomination? (continued)
After the review is complete, it will go on the bulk drug substance that are reviewed and not listed, the non-food-producing animal list (which we talked about is office stock), or the food-producing animal list (which is for antidotes for food-producing animals and sedatives and anesthetics for free-ranging wildlife). So, if it is on the bulk drug substance to be reviewed and not listed, we are still open to re-review the bulk drug substance at any time if new information has come up. And I just want to remind you again that these lists only apply when you are talking about office stock for non-food species (things that are on the shelves, that veterinary offices, office stock that's made in large batches), or those products that are made for food-producing animals and free-ranging wildlife. This does not apply in any way to patient-specific prescriptions for either individual patients or groups of animals that are being treated.

Slide 43: More nomination information
You can find more information— we do have a website on nominations, and it gives information about how to submit a nomination and more details about what we're asking for.

Slide 44: Implementation and Outreach
(Note, the FDA published updated implementation information in a letter to the American Veterinary Medical Association on September 9, 2022)

Another important thing to discuss is kind of how we plan to roll this out to everyone. As I said, it came out in April. Since that time, we have really emphasized stakeholder engagement. We have been looking for ways to get out there and speak to different people. We want veterinarians to understand what this means for them as well as pharmacies. I think another thing that's important to understand is that when we are looking to do inspections, and when we're looking to see if people are following the circumstances in the guidance, that means that we would be doing inspections at *pharmacies*. We do not intend to inspect veterinary offices to see if they if they are following this guidance unless the veterinary offices are the compounders themselves. This is really just aimed at the compounding and not veterinarians that prescribe compounded products. So we are looking to shift to those inspections later in fiscal year '23; during this time, we want to speak with people and help for there to be an understanding of really what the guidance means for everyone.

Slide 45: Key Points Under GFI 256
So, some of the key points I want to make sure I've been able to convey are that we really believe that veterinarians need this flexibility to compound from bulk drug substances. We know that there are not enough FDA-approved options available.

And I think something that I might have skipped over that probably impacts this group more is that in the guidance we did clarify that indexed and conditionally approved products can be used to compound instead of bulk drug substances. We see there being a hierarchy for compounding. So, our preference is that people use an approved product when it's available, because we know that there's known safety and efficacy. After that, if people need to turn to an indexed product or a conditionally approved product, this is one time when there is an exemption in the extra-label use not being allowed in those products. So, you can compound from index or conditionally approved products. We would like for the last resort to be bulk drug substances because we have the least amount of information about them.

And prescribing drugs to be compounded from bulk drug substances for specific non-food-producing patients or groups of non-food-producing patients is not limited to a bulk drug list. So those lists only apply to office stock or compounding for food animals. And also, medical rationales are only required in prescriptions if you're doing a copy of the product. A medical rationale could be something as simple as "would need too many pills". We do not intend to go back and to question the professional judgment of why this is needed; we just need to make sure that there has been a thought process and that there's a reason why a copy is being made.

Our nominations remain open, and that's also a rolling process. So, all of those lists are open. As we get things in, we're putting them on the "currently-under-review" list. We are giving enforcement discretion

for things that are on the "currently-under-review" list, and as we review them, we're hopefully getting them on to the right non-food or food-producing lists so that veterinarians can have access to them. I think that I skipped through a little bit faster than normal, so I'm happy to answer any questions. And I can turn that back over.

Slide 46: Question 1: Can mouse buprenorphine be used in other related rodents such as wild mice, voles, or other non-*Mus* mice? If the insert says for use in mice only or rats only and it is used in another species, is this off-label use or is it illegal?

>> Cate Pritchard: Thank you. Yes, as Nicolette starts sharing — we did receive a lot of questions in advance of the webinar, so we're going to be answering these first. Then there are some really good questions also coming in through the Q&A box; so as we have time, we'll be getting to those too. Nicolette, whenever you're ready, go ahead.

>> Nicolette Petervary: Perfect, thank you. So, we did get some questions in advance of this webinar. And question number one is: Can mouse buprenorphine be used in other related rodents such as wild mice, voles, or other non-*Mus* species? If the insert says for use in mice only or rats only, and it is used in other species, is this off-label use or is it illegal?

>> Dorothy Bailey: I will take that question. So, I'm assuming that the mouse buprenorphine question is in relation to the indexed product. It is true that extra-label use of indexed drugs is prohibited. That being said, if it says rats and mice on the label of an index product, then any rat, any mouse, would be acceptable. There is also an approved feline buprenorphine product that has a 24-hour effectiveness (it's once a day) that could be used legally. If you follow the actual label use regulations, that could be a legal extra-label use of that product.

Slide 47: Question 2: If 2 pharmaceutical grade drugs are missed by a licensed veterinary compounding pharmacy, are they still considered pharmaceutical grade? What if this is done by a university or hospital pharmacy? How about by the vet or PI?

>> Nicolette Petervary: Thank you. So, we'll go on to this next question, and there's a little bit to unpack here. If two pharmaceutical grade drugs are mixed by a licensed veterinary compounding pharmacy, are they still considered pharmaceutical grade? What if this is done by a university or hospital pharmacy, and how about by the vet or the PI?

And to reiterate, for the purposes of this session, we consider a pharmaceutical grade substance to be any active or inactive drug, biologic, or reagent manufactured under good manufacturing practices, which is approved, conditionally approved, or indexed by the FDA.

So, when you're mixing two pharmaceutical grade drugs, all components still meet this definition of pharmaceutical grade. But the real question really isn't the status of whether it's pharmaceutical grade or not. The question is, is this legal, extra-label use under the FDA? Because as we've mentioned before, OLAW's expectation is that institutions follow FDA guidance where applicable. So, as Dr. Bailey mentioned, for two approved drugs, it is legal extra-label use under the supervision of a licensed veterinarian or pharmacist. But remember that there are different requirements for indexed and

conditionally approved drugs, because extra-label use is prohibited. And I will pass this on now to our FDA speakers to see if they have any additional comments.

>> Amber McCoig: One I think I would just add: extra-label use is generally prohibited for those products, but for the purposes of compounding, we do allow discretion that they can be used if that can be instead of a bulk drug substance. So, this is one time when extra-label use of an index product is not going to be a concern for FDA.

>> Nicolette Petervary: Thank you. And one other point to once again reiterate is that the FDA requirements apply to *clinical care*. If the drug that is in question is a test article or the subject of the research, these requirements do not apply, these FDA requirements. So, just wanted to reiterate that before we go on to question number three.

Slide 48: Question 3: Is a cocktail such as ketamine-atropine-rompun (all vet pharmaceutical grade) still pharma grade when combined? If one component is not pharmaceutical grade, would the mixture also not be?

This is kind of a variation on the previous question. Is a cocktail such as ketamine-atropine-rompun, all veterinary pharmaceutical grade, still pharmaceutical grade when combined? If one component is not pharmaceutical grade, would the mixture also not to be?

So again, this is mixing apples and oranges. Pharmaceutical grade is a separate definition from the FDA definitions that have been used in this presentation. If all components that are mixed meet the definition of pharmaceutical grade, they would meet that definition, whether in combination or singly. If one mixture is not pharmaceutical grade, then the entire mixture would not be pharmaceutical grade. But the real question once again, here, is: Do FDA requirements apply? Is this legal, extra-label use? And once again, I will go back to the FDA speakers for their comments. And if you can also comment about the requirement for supervision for a licensed vet or pharmacist under certain circumstances.

>> Amber McCoig: Sure. In this case, these are all approved products, so that would fit under extra-label use compounding, which those provisions are provided under AMDUCA. If any of these were unapproved drugs… if it's an approved drug, then it fits; if all of them are approved drugs, then it fits under extra-label use. If any of them— much like with the pharmaceutical grade, if even one of them is not an approved drug, then that would be compounding a bulk drug substance. So then that would fit under Guidance 256 and the circumstances that are outlined there. It's important to remember that AMDUCA is very specific that compounding needs to occur by a pharmacist or a veterinarian. The language is *under the supervision of*, so that is expected that the veterinarian is involved, but not that the veterinarian is doing the compounding themselves necessarily. And the same applies to the guidance for compounding from bulk drug substances. A veterinarian or a pharmacist should be giving direction on the compounding, and may be involved in the decision, but they do not have to actually be doing the compounding themselves.

Slide 49: Question 4: Is sterile dilution of pharmaceutical grade drugs considered compounding? If a pharmaceutical grade diluent such as sterile saline or PBS is used to dilute a pharmaceutical grade drug, is it still pharmaceutical grade? Or does it need to be scientifically justified and approved by the IACUC? What about drugs that are sold in vials with the diluent attached to lyophilized powder?
>> Nicolette Petervary: Thank you. So, the next question is: Is sterile dilution of pharmaceutical grade drugs considered compounding? If a pharmaceutical grade diluent such as sterile saline or PBS is used to dilute a pharmaceutical grade drug, is it still pharmaceutical grade? Or does it need to be scientifically justified and approved by the IACUC? What about drugs that are sold in vials with the diluent attached to lyophilized powder?

So again, for our purposes, pharmaceutical grade definitions are different from approved, conditionally approved, or indexed drugs. And if all mixed components meet the definition of pharmaceutical grade alone or in combination, then they would still be considered pharmaceutical grade by the definition I gave previously. The question, again, is really— legal, extra-label, or compounding use, if this is considered compounding. And once again, I'll pass this along to my FDA colleagues.

>> Amber McCoig: So, in most cases, for sterile dilution to be added to an approved drug, that would be compounding under extra-label use. That is because it's mixing or changing of a product. But that would be legal under AMDUCA in most cases. In a situation when it's attached to the vial and it's part of the label, that's just legal use of the product. So that's covered by the label. And we would only apply, again, 'compounding from a bulk drug substance' if something was being used with an active ingredient that was not an approved product.

Slide 50: Question 5: A PI has received an FDA approval for an investigational new animal drug. If the application proposes to administer a dietary supplement that is non-USP grade on study, does that FDA approval confer some USP grade designation to the supplement for the purposes of administration to the animals? Or does the PI still need to justify use of a non-pharmaceutical grade substance? Does the FDA Approval for the INAD mean the supplement is "conditionally approved"?
>> Nicolette Petervary: Thank you. So, question five: A PI has received an FDA approval for an investigational new animal drug. If the application proposes to administer a dietary supplement that is non-USP grade on study, does that FDA approval confer some USP grade designation to the supplement for the purposes of administration to the animals? Or does the PI still need to justify use of a non-pharmaceutical grade substance?

Well, from the OLAW perspective, it sounds like the supplement is the test article under study, and that would be the scientific justification for its use. Regarding the follow-up questions on FDA approval, being considered as conditionally approved, I'll leave that to my FDA colleagues.

>> Dorothy Bailey: Yeah. So being a principal investigator under an INAD does not mean something is conditionally approved. What it means is that you are conducting research that the FDA will review to support an approval or a conditional approval. So, you should follow whatever protocol has been provided to you by the drug manufacturer who is seeking the approval or conditional approval, and then just collect all of the data, and then understand that that data is going to go to the FDA to be reviewed at some point.

Slide 51: Question 6: What is the status of buprenorphine and other analgesics as to shortages due to FDA enforcement actions?

>>Nicolette Petervary: Okay. Thank you. So, here's another question: Regarding buprenorphine, what is the status of buprenorphine and other analgesics as to shortages due to FDA enforcement actions? And I'll let my FDA colleagues...

>> *Dorothy Bailey* Yeah, do you want to take it, Amber?

>> Amber McCoig: I can jump in. Sure, I can start. So, we have a shortage list of products, and those are drugs that are medically necessary that we are aware of that are in shortage, and buprenorphine is not currently on the list. We do have some information that previously there were some manufacturing issues and there was a delay in the product going to market. FDA worked with them to take care of these issues, I think both on the human side and also on the indexed product. I believe Dr. Bailey also assisted with that. So, we don't currently have any enforcement action that would be causing any shortages or any knowledge of a current shortage. But we do have a website, or a-- I thought we were going to share it. But we have - oh, there it is. We do have a mailbox. So, this is our animal drug shortages mailbox. If you have any question about if a product is not available, or if a product happens to be in shortage, you can use this mailbox. You can also use it to bring it to our attention so that we can contact the manufacturer and maybe see if there's something that we can help with.

Another thing that I am not sure that I did a good job of highlighting is that one of the reasons that you can compound from a bulk drug substance is if an approved product is not available. So, in the guidance, we go through and talk about different reasons that you can use a medical rationale to make a copy, and the unavailability of an approved product would be a reasonable medical rationale for doing a copy of an approved drug.

Slide 52: Please comment on Buprenorphine SR (Ethiqa) availability currently. A statement was made that "a pharmaceutical grade sustained release compound is available, but the supply is sufficiently unreliable to be unavailable". Is Zoopharm from Wedgewood Pharmaceuticals, a compounding pharmacy, an option?

>> Nicolette Petervary: Thank you. And another availability question: Please comment on buprenorphine SR, Ethiqa, availability currently. A statement was made that "a pharmaceutical grade sustained release compound is available, but the supply is sufficiently unreliable to be unavailable." Is Zoopharm from Wedgewood Pharmaceuticals, a compounding pharmacy, an option?

So, from the OLAW perspective, use of a compounded pharmacy product during periods of unavailability would be considered acceptable, providing that the compounding meets FDA requirements where applicable. And Dr. McCoig, Dr. Bailey, do you have anything to add?

>> Dorothy Bailey: I think we would agree with that. As Amber said, if the indexed or approved drug is not available, then that can be used as a rationale to make a copy. But if there is an indexed or approved drug available that can be used, we would obviously prefer that you use the product that we have reviewed some safety manufacturing effectiveness information on. Is there anything else, Amber? Ok.

Slide 53: Question 8: Is OLAW enforcing the use of Ethiqa over compounded buprenorphine SR? Is buprenorphine SR through the likes of Zoopharm acceptable for research animal use for FDA? For OLAW? Zoopharm is a veterinary compounding pharmacy. Is use of Ethiqa preferred as it is not compounded and developed for mice and rats?

>>Nicolette Petervary: Thank you. Okay, this one is for OLAW. Is OLAW enforcing the use of Ethiqa over compounded buprenorphine SR? Is buprenorphine SR through the likes of Zoopharm acceptable for research animal use for FDA? For OLAW? And then as a little bit of added information: Zoopharm is a veterinary compounding pharmacy. Is use of Ethiqa preferred as it is not compounded and developed for mice and rats?

So once again, from OLAW's perspective, we expect institutions to follow FDA guidelines where applicable, and Dr. McCoig talked a little bit about the hierarchy of how to address drug substances with the ones having had more evaluation being preferable. I'd like to pass that over to you for a recap of that.

>> Amber McCoig: When you're looking to use something in an extra-label manner, certainly under AMDUCA you would use the approved product. If you're looking to compound a product and it needs to be mixed or altered in any way, then we really would prefer that the approved product be considered first, because that's gone through that pre-market review. It also has the post-market monitoring that we feel is able to alert us if there is a problem so that we can make sure that it does not get to too many animals. But we also recognize that it's possible that you may need to use a conditionally approved product or an indexed product. So that's kind of the second tier if there's not an approved product available, and then the bulk drug substances would be the next thing that you would look to.

Slide 54: Question 9: The manufacturer of buprenorphine SR has an expiration date of at least six months, but also a note to discard 28 days after vial puncture. Which takes precedence? OLAW and USDA ask institutions to follow manufacturer's recommendations to discard after 28 days unless there is an IACUC-approved reason to deviate. There is a 2022 JAALAS paper demonstrating extended sterility. What is FDA's take on this?

>> Nicolette Petervary: Thank you. And then question nine: The manufacturer of buprenorphine SR has an expiration date of at least six months, but also a note to discard 28 days after vial puncture. Which takes precedence? OLAW and USDA ask institutions to follow manufacturer's recommendations to discard after 28 days unless there is an IACUC-approved reason to deviate. There is a 2022 JAALAS paper demonstrating extended sterility. What is FDA's take on this?

Before I hand it over to Dr. McCoig and Dr. Bailey, I will just say that from the OLAW perspective, we concur with USDA, and we also expect that the most stringent requirement is applied. This is important for the maintenance of sterility and efficacy. And one study may not reflect all usage and storage situations across all institutions. So I would be very careful not to extrapolate from one paper to all institutions and all usage scenarios. And now if FDA would like to weigh in?

>> Dorothy Bailey: I would say we concur with OLAW's take on this. And in general, we would always recommend following the label instructions regarding expiration dates and when to discard. Yeah.

Slide 55: Question 10: I've heard from a clinician that buprenorphine SR has been reported to be causing abscesses at the injection site. Any reports to FDA on this?
>> Nicolette Petervary: Thank you. So, question ten: I've heard from a clinician that buprenorphine SR has been reported to be causing abscesses at the injection site. Any reports to FDA on this?

>> Amber McCoig: So, I am not aware of this, but this information can be obtained through a FOIA request. And that's generally how we release any of our adverse event information.

Slide 56: Question 11: We've just received a report that carbon dioxide supplies for euthanasia are currently low. Does FDA have any comment on the availability of medical grade gases? For oxygen, we've been advised in the past that welding grade gases are often superior to medical grade, as impurities would harm the stability of a welded joint, so the quality control is even better.
>> Nicolette Petervary: Thank you. And question 11: We've just received a report that carbon dioxide supplies for euthanasia are currently low. Does FDA have any comment on the availability of medical grade gases? For oxygen, we've been advised in the past that welding grade gases are often superior to medical grade, as impurities would harm the stability of a welded joint, so the quality control is even better.

>> Amber McCoig: We do not have an approved CO2, so we are not aware of any issues with the supply. With the availability of medical grade gases, that would be something that if we're not aware of any issues with availability, you can utilize that shortage mailbox for more information. We're also able to work with the other centers to determine if something that is under them is in shortage. And I think that we would always recommend medical grade when you're treating animals over something that's non-medical grade.

Slide 58:
>> Nicolette Petervary: Thank you. I think those were all the questions that we had. So now I will go into the Q&A box. We have one question. Is "conditionally approved" similar to "approved for emergency use", for example, when the COVID vaccine was approved for emergency use?

>> Dorothy Bailey: No, conditional approval is strictly for animal drugs. And it's an incentive that was provided initially in the Minor Use and Minor Species Animal Health Act of 2004 specifically to promote drug companies to actually get drugs approved for minor for minor species or for minor uses in major species. So, it's only in relation to the animal drug approval process. And like I said, all requirements have to be met except for effectiveness. So emergency use would be different. Yeah.

>> Nicolette Petervary: Okay, thank you. We are running out of time, so I'm just going to add this one last question, and we'll append the rest of the transcript. Is there a definition of "small group", and I think this refers to small groups of animals as opposed to, like, individual prescriptions or bulk office stock?

>> Amber McCoig: I think it's important to remember that we're only talking about therapeutic treatments. So, none of this would apply to investigational treatments. But for small group, it can be

defined as needed— so a herd could be a small group, a room could be a small group. We don't limit it with the definition.

>> Nicolette Petervary: Okay, thank you. We will get the rest of the questions answered and appended to the transcript once we have the materials formatted for accessibility, and there will be a newsflash and a listserv announcement making you aware of this. So, stay tuned for that in the future. Our next OLAW webinar will be in the winter, in December, with a topic to be determined. I hope you all join us at that time. Thank you.

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