Nine months in with the veterinary feed directive: Experiences and what is next

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Abstract

Last year at this time we were preparing for the Veterinary Feed Directive (VFD) transition and now we are survivors. There have been countless conversations between veterinarians and clients related to label indications, extralabel use, durations of use, concurrent use, repeated regimens (pulses), "hand fed" vs approved free choice feeds, and what comes next. We have advanced to the point of at least clarifying the uncertainties related to these subjects, and there is an indication of the next regulatory focus related to in-feed drugs. The "Blue Bird" labels have become familiar to many veterinarians to clarify the legal inclusions of Type C feeds. Also, Compliance Policy guide 615.115 has been useful for understanding the ability to use in-feed drugs in an extralabel manner in minor species. It is now clearly understood that a second administration of an approved in-feed drug regimen to an animal requires an additional VFD be written. For determining which drugs may be concurrently fed together in feed, the Blue Bird labels and the Feed Additive Compendium are key sources. Next in the regulatory lineup is an evaluation of medically important in-feed antibiotics for which there is not a defined duration of administration in the label regimen.

Key words: VFD, Guidance #213

Résumé

L'année dernière à pareille date nous nous préparions pour la transition engendrée par les directives concernant les aliments vétérinaires (VFD) et nous sommes maintenant des survivants. Il y a eu de nombreuses discussions entre les vétérinaires et les clients en ce qui concerne les indications homologuées, l'utilisation hors homologation, la durée de l'utilisation, l'usage concomitant, les schémas thérapeutiques répétées, les aliments distribués manuellement par rapport aux aliments approuvés en système d'alimentation libre et sur la suite des événements. Nous avons progressé à tel point qu'il est possible à tout le moins d'apporter des clarifications sur les incertitudes associées à ces sujets et il y a des pistes concernant vers quoi tendront les règlements sur les médicaments dans les aliments. Les étiquettes '*Blue Bird*' sont devenues familières auprès de plusieurs vétérinaires et clarifient les inclusions légales d'aliments du type C. Le guide de politiques de conformité 615.115 a été très utile pour mieux comprendre l'utilisation non-indiquée sur l'étiquette de médicaments dans les aliments chez les animaux de moindre importance. Il est maintenant clairement établi qu'une seconde administration d'un schéma thérapeutique approuvé de médicaments dans les aliments pour un animal requière l'écriture d'une nouvelle directive concernant les aliments vétérinaires. Les étiquettes '*Blue Bird*' et le recueil d'additifs alimentaires sont des éléments clés lorsque qu'il faut déterminer quelles drogues peuvent être utilisées dans l'alimentation en même temps. Prochaine sur la liste d'attente des règlements à établir sera l'évaluation des antibiotiques médicalement importants dans les aliments des animaux pour lesquels il n'y a pas de durée d'utilisation bien établie homologuée.

Introduction

Last year at this time we were preparing for the Veterinary Feed Directive (VFD) transition, and now we are survivors. Of the 292 new animal drug applications initially affected by Guidance for Industry #213, 84 were completely withdrawn, 93 oral-dosage form drugs for water administration were converted to prescription, and 115 applications were converted from over- the-counter, in-feed use to requiring a VFD.[6] There were 31 applications from which a production (e.g., growth promotion) claim was removed.

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Label Indications

The year 2017 will be remembered as a crash course in the details of label indications for medically important antimicrobials administered in the feed and water of food animals. Good sources for information have been the Compendium of Veterinary Products (online or phone apps),[4] company web sites, the Feed Additive Compendium,[8] and the "Blue Bird" label site from the Food and Drug Administration Center for Veterinary Medicine (FDA/CVM).[2] All are accessible with a web search or at the addresses listed in the references below. The Feed Additive Compendium requires a subscription, but has also been a good excuse to stop by your local feed mill to go over labels and how VFDs will be written and provided. On

the Blue Bird site, be sure to look over all cattle use classes if you at first don't find the indication you are looking for.

Extralabel Use

Every veterinarian can tell you that extralabel use is not allowed for drugs administered to major veterinary species in the feed. Major species include cattle, swine, turkeys, chickens, dogs, cats, and horses. However, there is a provision for extralabel use in minor species, which would include animals such as sheep, goats, chukars, partridges, quail, pheasants, fish, and captive cervids. This provision for extralabel use applies to none of the major species, meaning that a veterinarian may not authorize extralabel use of a drug through the feed to dogs, cats, and horses even though they are not food animals.

Detailed instructions for how a VFD is written for extralabel use in minor species are included in Compliance Policy Guide 615.115.[5] A noted limitation is that extralabel use is only permitted in mammals for another feed drug approved in a mammalian species, for birds only for another feed drug approved for an avian species, and in fish only for another drug approved in fish.

Duration of Use and Repeated Regimens (Pulses)

The key thing to look for on a label is the difference in the phrases "feed for up to...." and "feed continuously for....". The first phrase gives a veterinarian the option of authorizing the use of any period up to the maximum number of days. The latter phrase allows only use for the number of days on the label.

A common question has been for regulatory guidance in the "pulsing" of an in-feed drug. Pulsing is repeating of a label duration of an in-feed drug after a period of cessation of administration. There is no official regulatory document giving guidance for this practice. The following is an excerpt from a public letter in response to questions related to swine in-feed drug uses.[a]

> "Question: This is a common scenario: producer A wants to feed 2 pulses of chlortetracycline (CTC) in the nursery phase (8 week duration of growth). In a single group of a 1,000 pigs, they get 2 weeks of CTC at the beginning (weeks 0-2 at 15 lb of weight) and again the last 2 weeks of the group (weeks 7-8 at 60 lb of weight). How many VFDs are required for this group?
> Answer: A veterinarian cannot issue a V FD that authorizes a duration of use that is inconsistent with the directions for use described on the product labeling. In the example provided, if the approval limits the treatment to 14 days, the VFD can only authorize that approved duration. Issuing a VFD that authorizes a 14-day course to be repeated for the same animals would be considered an illegal extralabel use.
>
> However, if the veterinarian reassesses the animals involved after a single course of therapy (i.e., drug administered according to the labeled dose and duration), the veterinarian may decide that additional therapy is warranted. In such case, a new VFD is needed."

There is no regulatory guidance for a required period between administrations, or the level of justification for another administration, other than the veterinarian deciding the continued administration is necessary. It is quite clear that an animal only appears on a VFD once, and any additional administrations require an additional VFD.

Concurrent Use

The package label and labels available on web resources for in-feed VFD drugs do not contain concurrent clearances. These concurrent feeding approvals may be found in the Feed Additive Compendium, by reviewing the Bluebird Labels available from the FDA/CVM (remember to be sure you are looking in the right use class on the website), or by contacting company representatives.

In cattle, a common focus of conversation has been that chlortetracycline is not approved for concurrent feeding with monensin or tylosin. Also, amprolium does not have a concurrent clearance with any in-feed drug.

"Hand Fed" vs Free-Choice Feeds

In the author's experience over the last year and a half, the most common questions have concerned free-choice feeds. A mineral feed (or any feed) may only be labeled as a free-choice feed when both the drug label and the feed formulation have been approved for this indication by the Food and Drug Administration Center for Veterinary Medicine (FDA/CVM). In the case of a free-choice feed, the intake is determined by the feed formulation, and the animal's subsequent intake of that formulation, rather than by the amount provided each day. In other words, the intake of the drug (the dose) is determined by the feed ingredients, the formulation of these ingredients, and the concentration of the drug. Therefore, the formulation of a free-choice feed must be approved by the Food and Drug Administration Center for Veterinary medicine. This approval includes manufacturing and intake considerations.

This term "hand fed" has been a source of confusion. From a regulatory standpoint, the designation "hand fed" on a feed drug label is added during the approval process when there is concern for adverse drug reactions, and the feed is required to be fed daily in order for the animals to be observed daily. It refers to the drug, not the formulation. This designation is most commonly applied to a feed to be fed on pasture.

In common industry use, the terms "hand fed" and "limit fed" have been used to describe feeds fed on a daily

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basis, whether once or multiple times a day. This is an understanding of the terms based on how the feed is fed (at least once daily).

Regardless of how "hand fed" is interpreted in common use, it is clear that the term "hand fed" is not the same as free choice, and that the term free choice stands out alone as having an approved drug label provided combined with an approved feed formulation. Both the drug and the formulation must be approved for the free-choice application. The same approved free-choice drug may be marketed in multiple approved free-choice formulations.

In the past, unapproved medicated mineral formulations have been manufactured and marketed as "free choice" feeds without regulatory intervention. Regardless of wording on the feed tag, these formulations were clearly meant to be fed in a free-choice manner. In these cases, the term "free choice" was not based on an FDA approval.

Regardless of terminology, feeding a medicated mineral feed other than in a manner of daily feeding meets the definition of free-choice feeding, and the drug and formulation must be approved for such use. If an unapproved drug regimen, and/or an unapproved free choice feed formulation are used to manufacture a medicated mineral feed (or any feed) with the intended use of being fed in a free-choice manner, then that drug and the feed are considered adulterated by the FDA/CVM.

Type A Medicated Articles and Distribution

Type A medicated articles may contain a concentration of the in-feed drug up to 200 times the concentration in the final Type C feed. The Type A medicated article does not have nutritive content, so therefore is not a feed, and the article itself does not require a VFD for sales or distribution. However, any Type B or Type C feed created from a Type A medicated article is subject to the VFD rule.

Some distributors have required that documentation be provided by the purchaser of a Type A medicated article documenting that they are aware of the need for a VFD to feed the drug to food animals. Some have gone so far as to insist on seeing or having a copy of the VFD which will allow feeding of the drug.

Obtaining a Type A medicated article and then feeding it without the appropriate VFD is an illegal act.

What's Next?

In a September 12, 2016 CVM update, and a Federal Register notice dated soon thereafter, the FDA/CVM asked for input on the approximately 32% of therapeutic products affected by Guidance for Industry #213 which do not have a defined duration of use.[7,10] The agency asked for further information on...

- The underlying diseases requiring these drugs for therapeutic purposes, and periodswhen livestock or poultry are at risk of developing these diseases;
- More targeted antimicrobial use regimens and husbandry practices that may help avoid the need for these antimicrobials, or that may help make more targeted antimicrobial use regimens more effective; and
- Strategies for updating affected labeling of drug products that do not currently include a defined duration of use.

The specific indication/disease and ingredient(s) for which information was requested related to cattle were as follows:

- anaplasmosis - chlortetracycline
- bacterial enteritis - chlortetracycline, oxytetracycline
- liver abscesses - chlortetracycline, tylosin, oxytetracycline, neomycin with oxytetracycline, virginiamycin
- pneumonia - chlortetracycline

As of this writing, the comment period has closed and comments are being considered by the FDA/CVM.

In addition to major regulatory changes from the FDA/CVM, the progression of state regulations beyond federal regulations has occurred. California was the first, with the passing of Senate Bill 27 in 2016. The bill goes further than Guidance for Industry documents #209 and #213, in that all medically important antibiotics will require a prescription or VFD.[3] Selected language from the bill is as follows:

"**14401**.

Beginning January 1, 2018, a medically important antimicrobial drug shall not be administered to livestock unless ordered by a licensed veterinarian through a prescription or veterinary feed directive, pursuant to a veterinarian-client-patient relationship that meets the requirements of Section 2032.1 of Title 16 of the California Code of Regulations.

14402.

(a) Beginning January 1, 2018, a medically important antimicrobial drug may be used when, in the professional judgment of a licensed veterinarian, the medically important antimicrobial drug is any of the following:

(1) Necessary to treat a disease or infection.

(2) Necessary to control the spread of a disease or infection.

(3) Necessary in relation to surgery or a medical procedure.

(b) A medically important antimicrobial drug may also be used when, in the professional judgment of a licensed veterinarian, it is needed for prophylaxis to address an elevated risk of contraction of a particular disease or infection.

(c) A person shall not administer a medically important antimicrobial drug to livestock solely for purposes of promoting weight gain or improving feed efficiency.

(d) Unless the administration is consistent with subdivision (a), a person shall not administer a medically important antimicrobial drug in a regular pattern."

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Notice that section (d) indicates that only in cases consistent with section (a) is a person able to administer a medically important antimicrobial drug in a regular pattern; prophylaxis is not included in section (a). The bill also requires the state to collect and report medically important antimicrobial use data.

On May 31, 2017, Maryland became the second state to address the administration of antimicrobials to food animals "in a regular pattern" in SB0422 and HB0602, with language very similar to California.[9] Each year the state is required to collect "publicly available data on the use of medically important antimicrobial drugs in cattle, swine, and poultry."

Legislators in Oregon introduced SB785 and HB2396 in 2017.[1] These bills require a livestock producer operating a concentrated animal feeding operation as defined by the EPA to file an annual report including the number of animals and the total amount, dose, length of time, disease, and purpose (prevention, control, or treatment) for which medically important antibiotics were used in their operation. Language in the bill also states... "Information reported under this section is a public record, and notwithstanding ORS 192.501 and 192.502, is not subject to exemption from disclosure". The bill, as available at the time of this writing, also requires that a licensed veterinarian must determine that the provision of the medically important antibiotics to the animal is necessary.

Conclusions

The last year has brought significant changes to the veterinary-client-patient relationship in relation to the use of medically important antimicrobials in the feed or water given to food animals. We can anticipate continued evolution in this area, with the next focus clearly on the duration of administration. Three states have passed or are deliberating changes in state law which impose varying combinations of more restrictions on use, more detailed medically important antimicrobial drug use reporting for food animals, and requiring veterinary authorization for all medically important antimicrobials in food animals, regardless of the prescription requirement status on the label.

Endnote

[a]Personal communication. September 6, 2016 letter to Dr. Christopher Rademacher from the Food and Drug Administration Center for Veterinary Medicine.

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