Professional Flexible Labeling Workshop II

Task Force Report

Developing a model of a professional veterinary drug label

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The following model label and supporting commentary reflects discussions that occurred during the December 1995 Professional Flexible Labeling Workshop II, which was cosponsored by the Food and Drug Administration/Center for Veterinary Medicine (FDA/CVM), the American Academy of Veterinary Pharmacology and Therapeutics (AAVPT), the Animal Health Institute (AHI), and the American Veterinary Medical Association (AVMA). This workshop represented another step in the ongoing cooperative effort to enhance the availability of animal drugs for therapeutic use and to expand animal drug labels, thereby providing veterinarians with the information needed to choose an appropriate course of treatment and facilitating greater flexibility of drug use.

The task force was composed of experts with a wide range of expertise, including veterinary drug regulation (MNM, GKH, LDR), academic pharmacology (GDK, JER), pharmaceutical development (SAB, DDC), and field practice (MGR). The task force members brought their individual experiences and expertise to the writing of this report. The content of the report does not necessarily reflect the opinion of the authors' respective associations nor endorsement by any academic institution, industrial company, or federal agency.

The task force recognizes that certain aspects of the model label and the associated comments may not be allowed under current laws and regulations. The professional flexible label (PFL) must, therefore, be viewed as a proposal for how labels can appear in the future, whether it fits existing laws and regulations. Similarly, modifications in the veterinary drug approval process must be viewed from the same perspective. This includes proposals such as the use of auxiliary databases and additional information as mechanisms by which to facilitate supplemental approvals.

The model label contains much of the original information provided in the FDA/CVM and AHI "strawman" labels that were presented at the December 1995 workshop. Therefore, credit for this report also must be given to individuals who helped draft these original labels. Persons responsible for drafting the FDA/CVM label include Drs. George Haibel (chairperson), John Baker, Joseph Bertone, Naba Das, William Flynn, Marilyn Martinez, M. Elizabeth Reese, and Tania Woerner. Persons responsible for drafting the AHI strawman labels include Drs. Charles Farho (chairperson), Scott Brown, Dennis Copeland, Rainer Muser, Mark Wood, Perc Reeve, and Mr. Robert Chesebrough.

We request that this task force report be critically reviewed by all interested parties. We solicit comments from all veterinarians and other individuals as well as groups who work in any segment of the animal health profession. Comments regarding the task force report should be submitted to Dr. Janis H. Audin via FAX (847-925-1329), Internet (74253.562@compuserve.com), or mail (AVMA, 1931 N Meacham Rd, Ste 100, Schaumburg, IL 60173). The task force will review, summarize, and respond to these comments in the Dec 15, 1996, issue of the *JAVMA*. Comments must be received no later than Aug 15, 1996.

Summary of Terms

During the Professional Flexible Labeling Workshop II, the idea was forwarded that a tiered approach should be taken to the labeling of veterinary drugs. The foundation of this pyramid consists of information required by statute to ensure public health (eg, human food safety, environmental protection) and safe and efficacious drug use. The other categories of information are intended to support therapeutic decisions. These differ by the degree

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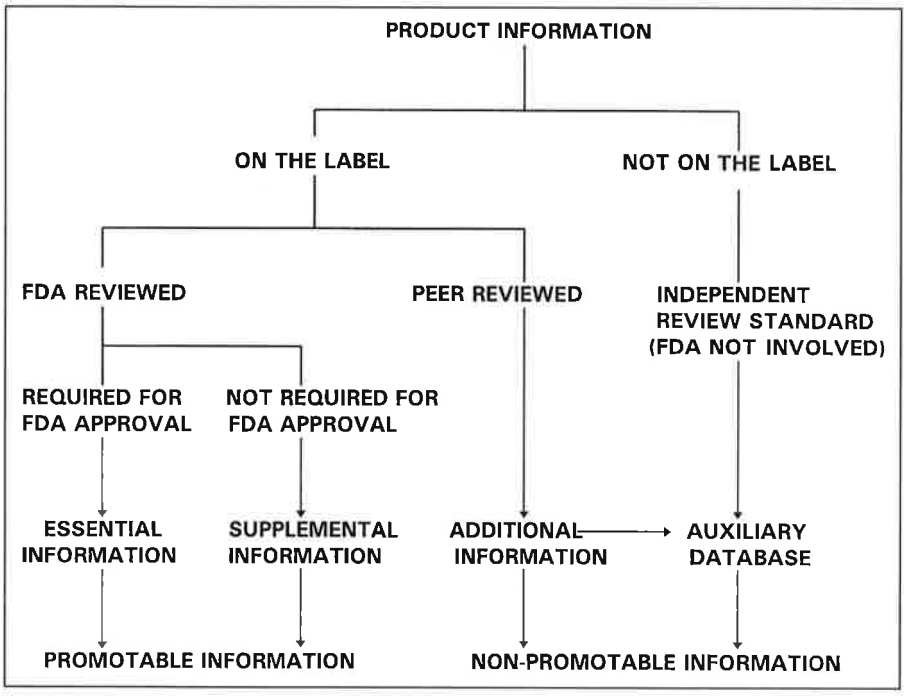

Figure 1—Proposed options for directing the flow of product information and its relationship to the veterinary drug approval process.

to which they are subjected to FDA/CVM review and by the degree to which they can be included in advertising and promotional materials (Fig 1).

The objective of this task force proposal is to provide practitioners with ready access to information that can impact their therapeutic decisions. This approach also is intended to provide a mechanism through which drug availability can be enhanced. This vision has generated a variety of concepts and terms that are defined as follows:

Essential information—information that is required for product approval. This information may be included in any advertising and promotional materials.

Supplemental information—optional information that supports therapeutic choices, provides guidance in product use, and has undergone review by the FDA/CVM. Although this information is not considered essential for product approval, it may be included in promotional materials.

Additional information—optional information that an impartial group designated as appropriate by the FDA/CVM has determined to be suitable for inclusion on the product label, but does not support an approved product claim. The determination of acceptability as additional information is made in a manner similar to the peer-review process of an editorial board. This information may not be included in product promotional materials.

Dosage range—a range of dosages and dosing intervals within which product safety and efficacy have been confirmed. For products intended for use in food-producing animals, adequate residue information is available to determine use conditions (withdrawal times) that ensure human food safety.

Label indication—a disease/condition for which product efficacy has been confirmed on the basis of FDA/CVM review of sponsor-submitted data.

On-label use—use of the drug product in the target animal species for a label indication and within the dosage range stated on the product label.

Within-label use—use of a product in the target animal species and within the dosage range stated on the product label, but for a disease/condition not included as a label indication.

Extra-label use—use of a product in another species or outside of the stated dosage range, frequency, route, or duration of administration, regardless of whether the use conforms with the label indication.

Promotion—for the purpose of this task force report, we will not differentiate between drug promotion and drug advertising. Drug promotion/advertising will be defined as any attempt by the drug sponsor to stimulate the use of their product for a particular disease, pathogen(s), or target animal species. Legitimate scientific interchange (eg, presentation of study data at scientific meetings) does not constitute promotion.

Product label—information on the package insert and all other parts of the label. The product label is approved by the FDA/CVM.

Auxiliary information—a compilation of drug use information from various sources, including published information that has been gathered for public dissemination. Individuals associated with auxiliary resources (databases) are not associated with the FDA/CVM. Information contained within an auxiliary information resource is not promotable by a drug sponsor.

ESSENTIAL INFORMATION

GORILLAMYCIN® INJECTION
brand of exoxysporin sulfate injectable solution

For subcutaneous injection in beef cattle

CAUTION: Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian. Any use of this animal drug must be in compliance with the prescribed use of the attending licensed veterinarian. Anyone involved in the unauthorized use of an animal drug is in violation of federal statutes.

DESCRIPTION

Each milliliter of GORILLAMYCIN® INJECTION contains an aqueous solution of exoxysporin sulfate equivalent to 200 mg exoxysporin activity.

INDICATIONS

GORILLAMYCIN® INJECTION is indicated for the treatment of bovine respiratory disease (BRD) (shipping fever, pneumonia) associated with organisms susceptible to exoxysporin sulfate (see MICROBIOLOGY section)[1].

EFFECTS

GORILLAMYCIN® INJECTION contains the sulfate salt of exoxysporin which is a rapidly absorbed bactericidal agent with activity against a wide range of Gram-negative and Gram-positive bacteria and *Mycoplasma spp.* Exoxysporin sulfate acts by binding to the 50S ribosomal subunit of susceptible bacteria, inhibiting translocation which results in a bactericidal effect. The activity of this compound is not inhibited by known bacterial enzymes and is favored in an alkaline environment.

DOSAGE AND ADMINISTRATION

GORILLAMYCIN® INJECTION is approved for use within the dosage range of 2 to 20 mg/kg body weight once daily (qd) when administered by subcutaneous injection to cattle. Efficacy has not been established at doses less than 2 mg/kg daily for 3 consecutive days (or a total dosage of 6 mg/kg during a 3-consecutive-day course of therapy). Alternatively, based upon pharmacokinetic/pharmacodynamic models, doses of 5 to 20 mg/kg may be administered qd or once every 48 hours (q48h), depending upon pathogen sensitivity (see Table IV).

GORILLAMYCIN® INJECTION must be administered in 3 to 5 repeated doses. Total drug exposure during a course of therapy is not to exceed 100 mg exoxysporin per kilogram of body weight (20 mg/kg times 5 consecutive daily doses). The upper dosage limit is based upon target animal safety data. The safety of exoxysporin when administered beyond 5 consecutive days of treatment has not yet been established.

Injection volume should not exceed 20 mL per injection site, and should be administered subcutaneously in the neck region.

RESIDUE WARNING Not for use in lactating dairy cows.

TABLE I. Withdrawal times for various dosage ranges

Dose (mg/kg BW)	Dose Frequency	Dosing Duration	Withdrawal Time
2 to 5	once daily	up to 5 days	zero
6 to 10	once daily	up to 5 days	3 days after last treatment
11 to 20	once daily	up to 5 days	5 days after last treatment

[1]Pathogens associated with the *in vivo* demonstration of clinical efficacy included *Haemophilus somnus, Pasteurella multocida* and *Pasteurella haemolytica.*

Withdrawal times have not been established for dosages greater than 20 mg/kg mg/kg BW and/or treatment durations of more than 5 days. Use of this product outside of these approved regimens may result in violative residues.

CONTRAINDICATIONS

GORILLAMYCIN® INJECTION (exoxysporin sulfate) is contraindicated in animals previously found to be hypersensitive to the drug or to have impaired renal function.

ADVERSE REACTIONS

The use of GORILLAMYCIN® INJECTION may result in mild signs of immediate and transient local pain to the animal if accidentally administered intramuscularly. Transient mild diarrhea and appetite suppression was observed in target animal safety studies when calves were administered 20 mg/kg body weight for 5 consecutive days. Administration of exoxysporin sulfate may cause transient lacrimation (for up to 1 hour).

PRECAUTIONS

The safety of GORILLAMYCIN® INJECTION in cattle intended for breeding has not been determined.

STORAGE CONDITIONS

Store at or below room temperature, 86 °F (30 °C).

HOW SUPPLIED

GORILLAMYCIN® INJECTION is supplied in multi-dose vials containing 100 mL, 250 mL and 500 mL.

WARNING

NOT FOR HUMAN USE. KEEP OUT OF REACH OF CHILDREN.

Avoid contact with skin and mucous membranes. Upon accidental exposure, thoroughly flush with water. Minor skin irritation on human subjects has been shown to occur with frequent exposure. Therefore, handlers should avoid skin contact with the injectable solution.

For further emergency information contact Regional Poison Control (1-800-321-8765) or Drugs-4-Ewes (1-800-000-0000).

For customer service, adverse effects reporting and/or a copy of the material safety data sheet (MSDS), call 800-23-4567.

NADA #000-000; approved by FDA

SUPPLEMENTAL INFORMATION

<chemical structure of exoxysporin sulfate>

GENERAL PHARMACOLOGY:

Exoxysporin is a lipid-soluble weak base with a pK_a of 7.6.

Figure 2—Task force example of a hypothetical product insert of a flexibly labeled prescription antimicrobial. The model label contains information on a fictitious macrolide-like compound (exoxysporin sulfate) developed for use in the treatment of bovine respiratory disease. Product insert continues on pages 86–88.

CLINICAL PHARMACOLOGY

MICROBIOLOGY

Date of original approval: 6/18/96
Updates:

Exoxysporin has been shown to have significant *in vitro* and *in vivo* activity against *P. haemolytica* and *H. somnus*, major bacterial organisms associated with BRD in cattle. The *in vitro* activity of exoxysporin against livestock bacterial and mycoplasmal pathogens is shown in Table II. In most cases, however, the clinical efficacy of this compound against diseases associated with these organisms has not been established. *In vitro* susceptibility (using NCCLS[a] standards) was determined for isolates collected during 1989 through 1995 from 18 veterinary diagnostic laboratories and universities located in the United States.

Table II. Susceptibility values for exoxysporin

Organism	Number Isolates	MIC Range	MIC_{90}	Source	Date of Isolation	Date of MIC_{90}
Actinobacillus pleuropneumonia	45	0.03 -0.125	0.06	P	4/95 to 8/95	6/96
Actinomyces pyrogenes	61	0.5-2	1	B	4/95 to 8/95	5/96
Bordetella bronchiseptica	40	0.5-2	1	P	4/95 to 8/95	4/96
Erysipelothrix rhusiopathiae	10	0.1-1.5	NA**	P	4/95 to 8/95	4/96
Escherichia coli[*1]	90	0.03 -0.125	0.06	B	4/95 to 8/95	3/96
Escherichia coli	50	0.03 -0.125	0.06	P	4/95 to 8/95	1/96
Haemophilus parasuis	10	0.03 -0.125	NA**	P	4/95 to 8/95	2/96
*Haemophilus somnus**	56	0.01 -0.06	0.03	B	3/89 to 8/95	6/96
Mycoplasma spp.	42	0.125-1	0.5	B	4/95 to 8/95	12/95
Mycoplasma spp.	21	0.125-1	0.5	P	4/95 to 8/95	10/95
*Pasteurella haemolytica**	104	0.03-0.125	0.06	B	3/89 to 8/95	10/95
*Pasteurella multiocida**	73	0.01-0.06	0.03	B	3/89 to 8/95	6/96
*Moraxella bovis**	58	0.01-0.06	0.03	B	4/95 to 8/95	4/96
*Fusobacterium necrophorum**	21	0.03-0.125	0.06	B	4/95 to 8/95	3/96
Pseudomonas aeruginosa	65	2-16	4	B	4/95 to 8/95	1/96
Salmonella choleraesuis	85	0.06 -0.5	0.125	P	4/95 to 8/95	6/96
Salmonella dublin	38	0.06 -0.5	0.125	B	4/95 to 8/95	3/96
Salmonella typhimurium	91	0.06 -0.5	0.125	B	4/95 to 8/95	2/96
Staphylococcus aureus[1]	34	0.125-0.5	0.25	B	4/95 to 8/95	2/96
Streptococcus suis	38	0.5-2	1	P	4/95 to 8/95	4/96

**In vivo* activity for these organisms has been demonstrated.
***MIC_{90}* determination Not Appropriate due to Insufficient Isolates.
[1]Not Isolated from mastitic dairy cattle.
Source species: B=bovine, P=porcine

Many strains of *Pseudomonas aeruginosa* have been shown to be resistant to exoxysporin. Although most anaerobic bacteria are resistant to exoxysporin, susceptibility has been observed for certain anaerobic pathogens. Exoxysporin bactericidal action differs from that of other antimicrobial agents such as aminoglycosides or beta-lactams; therefore, organisms resistant to these drugs may be susceptible to exoxysporin.

Table III. Interpretation of zone diameters and MICs for exoxysporin for use in cattle

Inhibitory Zone Diameter* (mm)	Interpretation**	MICs (µg/mL)
≥ 22	Susceptible (S)	1.0
17 - 21	Intermediate (I)	2.0 - 8.0
≤ 16	Resistant (R)	16.0

*Based on NCCLS[a] standard disk susceptibility tests with a 5-µg exoxysporin disk.

**Based upon the MIC or Zone Diameter for a bovine bacterial pathogen and the pharmacokinetics of exoxysporin in cattle.

[a]National Committee for Clinical Lab. Standards, Performance Standards for Antimicrobial Disk and Dilution Susceptibility Tests for Bacteria Isolated from Animals; Proposed Standard, Document M31-P, Vol. 14, No. 20.

A report of "Susceptible" indicates that the pathogen is likely to be inhibited by the generally achievable drug concentration in tissues using doses of 2 to 5 mg/kg. A report of "Intermediate" suggests the organism would be susceptible if a dosage of 6 to 20 mg/kg are used. A report of "Resistant" indicates the achievable drug concentrations are unlikely to be inhibitory and that other therapy should be considered (Table III).

PHARMACOKINETICS

All pharmacokinetic studies were conducted in feedlot cattle (heifers and steers) using an HPLC assay for parent exoxysporin with a limit of quantitation of 0.01 µg/mL. The assay does not distinguish between free and protein bound exoxysporin. Additional radiolabeled exoxysporin studies were conducted for metabolite identification and quantitation.

Absorption: Exoxysporin is rapidly absorbed from subcutaneous injection sites. Maximum plasma concentrations of approximately 0.16 µg/mL and 1.73 µg/mL are observed approximately 2 hours after a single subcutaneous dose of 2 and 20 mg/kg respectively. Studies demonstrate that nearly 100% of the administered dose is absorbed when given by subcutaneous injection.

Distribution: Exoxysporin is approximately 80% bound to a_1 acid glycoprotein within the range of 0.01-10 µg/mL of plasma. The apparent volume of distribution (Vd/F) is approximately 11 L/kg. Slightly but not statistically significantly lower Vd/F is observed at a dosing level of 20 mg/kg.

After a dose of 5 mg/kg to feedlot cattle, tissue homogenate concentrations of parent exoxysporin are highest in lung, reaching concentrations approximately 15 times higher than concurrent free and bound plasma concentrations followed by liver, kidney, fat, and muscle. Uninfected tissue cage fluid concentrations of exoxysporin approximate free plasma exoxysporin concentrations. However, infected (*Pasteurella haemolytica*) tissue cage fluid concentrations of exoxysporin exceed total (free plus bound) plasma exoxysporin concentrations. It has been suggested that protein binding may be enhanced at the site of infection, corresponding to the observed affinity for a_1-acid glycoproteins. The clinical significance of this observation has not been determined.

Based upon human food safety studies conducted at 20 mg/kg daily for 5 consecutive days, a half life of 12 ± 3 hours (mean ±SD) has been determined for the depletion of the marker residue

from the target tissue (liver) of feedlot cattle. Exoxysporin partitions extensively into the rumenoreticulum and milk as a result of ion trapping in those more acidic environments. Milk concentrations at the first milking after subcutaneous administration are 20 to 30 times higher than concurrent plasma concentrations, with extensive binding to milk proteins. Milk and plasma concentrations decline in parallel.

Metabolism: Exoxysporin is metabolized to several inactive metabolites and to N-demethylexomycin, the predominant metabolite in plasma. N-demethylexomycin comprises 5% of the total radioactivity and is approximately 15% as microbiologically active as parent exoxysporin against targeted pathogens. Metabolites are present in approximately the same ratios in plasma, milk, and lung. Higher ratios of metabolites compared with parent exoxysporin are present in bile, urine, and feces.

Excretion: Approximately equal concentrations of parent exoxysporin occur in bile and urine. However, because of the much higher urine flow compared with biliary flow, 75% of total drug is excreted in urine, and 25% is found in feces. Urine excretion is by glomerular filtration and tubular secretion with some passive reabsorption that is affected by urine pH. In cattle, the plasma terminal elimination half-life ($t_{1/2}$) is approximately 12 hours.

Plasma concentration-time profiles: Figures 1a and 1b show the mean plasma concentrations of parent exoxysporin in cattle after subcutaneous doses of 2 and 20 mg/kg (qd for 5 consecutive days or 20 mg q48h for 3 treatments). Pharmacokinetic parameter estimates are shown in Table V. Steady-state is achieved within the first 3 days of dosing, resulting in blood levels which are approximately 33% greater than those observed after a single administration.

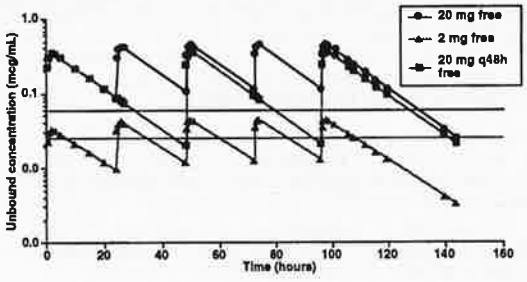

Figure 1a: Unbound exoxysporin plasma concentrations in cattle following multiple subcutaneous administrations of either 2 mg/kg or 20 mg/kg BW.

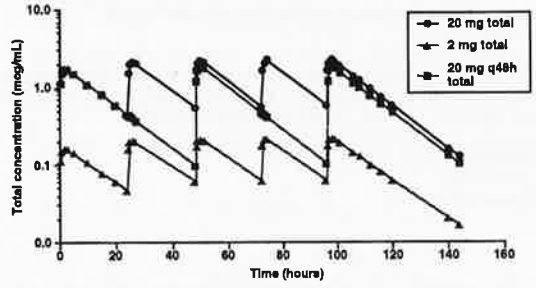

Figure 1b: Total exoxysporin concentrations in cattle following multiple subcutaneous administrations of 2 or 20 mg/kg BW.

Pharmacokinetic/pharmacodynamic relationships: Preliminary evaluation indicates that exoxysporin antibacterial activity is dependent upon time above MIC. Prolonged and persistent *in vitro* postantibiotic effects were observed with most susceptible organisms (Jones AA, Jones BB, Jones CC. Pharmacodynamic evaluation of antibacterial agents in man and cattle. *Journal of Antimic. Use.*, 19XX; Vol 1:1-10). Simulation-based time above MIC estimates (based upon observed linear plasma protein binding) with qd and q48h dosing regimens are provided in Table IV.

Age differences: In cattle from two months of age to sexual maturity, there were no demonstrable age differences in plasma disposition of parent exoxysporin.

Table IV. Estimated time (hr) above MIC levels of 0.06 and 0.03 µg/mL for free exoxysporin in feedlot cattle with different dosage regimens

	Single Dose		Steady State			
			given qd		given q48h	
Dose (mg/kg)	0.03	0.06	0.03	0.06	0.03	0.06
2	3	0	8	0	BAD[a]	BAD[a]
3	10	4.5	16	7	10	5
5	19	7	23	24	21	9
15	36	25	24	24	37	26
20	41	30	24	24	42	31

[a]Below Approved Dosage of 2 mg/kg/day for 3 consecutive days.

Table V. Pharmacokinetic (PK) values for total exoxysporin (free and bound) in plasma of feedlot cattle after a single subcutaneous dose of 2 and 20 mg/kg

	Dose (mg/kg)	
PK Values	2	20
Vd/F[a] (L/kg)	11	10.2
k_a (hr^{-1})	2.0	1.7
K (hr^{-1})	0.057	0.063
C_{max} (µg/mL)	0.164	1.73
T_{max} (hr)	1.83	2.01
AUC_{0-24} (µg°hr/mL)	2.35	24.0
AUC_{0-48} (µg°hr/mL)	2.99	29.5
$T_{1/2-K}$ (hr)	12	11.0
$t_{1/2-ka}$ (hr)	0.3466	0.4077
C_{24h} (µg/mL):		
Total	0.048	0.4077
Free	0.0096	0.09
C_{48h} (µg/mL):		
Total	0.012	0.099
Free	0.0024	0.02
Protein Binding (%)	80	80

a: apparent volume of distribution = F*dose/(K*AUC_{0-inf})
where F = bioavailability relative to an intravenous dose and
K = apparent terminal elimination rate constant (= $0.693/t_{1/2-K}$)
AUC = area under the plasma concentration/time curve
C_{24h} = exoxysporin concentrations at Hour 24 post-dose
C_{48h} = exoxysporin concentrations at Hour 48 post-dose

EFFICACY (Studies conducted to establish label indications)

The efficacy of exoxysporin against naturally occurring BRD was demonstrated in a clinical study involving five different feedlots. A total of 1000 feeder cattle weighing approximately 400 lb and demonstrating clinical signs of BRD were administered exoxysporin subcutaneously at a dose of 2 mg/kg for 3 consecutive days. Efficacy was demonstrated by a significant reduction in mortality (2% vs. 15%), increased clinical cures (78% vs. 64%) and reduction in relapses (12% vs. 22%) when compared to non-treated controls. Pathogens associated with in-vivo cure include *Haemophilus somnus*, *Pasteurella multocida* and *Pasteurella haemolytica*. In these trials, no drug-related adverse effects were observed.

TOXICOLOGY

Acute safety studies were conducted in rats with no adverse effects noted at doses up to 1000 mg/kg of body weight. Ninety-day feeding studies in dogs and rats concluded that there were no observable untoward effects at treatment rates of 200 and 100 mg/kg respectively. Chronic studies in rats and mice verified no adverse effects at 20 and 200 mg/kg. Exoxysporin was determined to be noncarcinogenic.

A two-generation rat reproduction study displayed no evidence of impaired fertility at doses of 200 mg/kg. No teratogenic effects were observed in rabbits at doses of 50 mg/kg or in rats at 100 mg/kg. However, there are no adequate and well-controlled studies in cattle intended for breeding.

TARGET ANIMAL SAFETY

Results from a study in normal feeder calves receiving 2, 20 and 30 mg/kg body weight of exoxysporin sulfate daily for 15 days revealed no adverse effects at 2 mg/kg BW; appetite suppression by day 5 in 2 of 10 calves receiving 20 mg/kg BW; and mild diarrhea and appetite suppression in all calves receiving 30 mg/kg BW. All other clinical signs were normal. Results of clinical pathology and hematology in the 30 mg/kg BW group demonstrated electrolyte imbalance and abnormalities consistent with the clinical signs observed.

In an injection site tolerance study, 20 and 60 mL of product were administered subcutaneously (1X and 3X the recommended volume per injection site). Evaluations were conducted at 1, 7, 14, 21, and 28 days following injection. Although histopathological evaluation of injection sites show the solution to be a slight tissue irritant, no lesions were observed upon gross post-mortem examination at 7 days post-injection. In contrast, exoxysporin sulfate has been found to be irritating after intramuscular administration. At 1X and 3X the recommended volume, myonecrosis and sterile abscess formation occurred and were noted within 3 days of injection. At 28 days after injection, fibrosis and significant scar formation were still evident, although minimal necrosis and no abscesses remained.

ADDITIONAL INFORMATION

(Information contained within this section is provided solely for consideration by the veterinary practitioner. This information does not reflect FDA-approved claims or indications.)

During BRD clinical studies, an outbreak of infectious bovine kerato-conjunctivitis (pink-eye) associated with *Moraxella bovis* occurred. Seven cases occurring in the treated animals responded satisfactorily with no additional treatment, while 7 of the 9 cases in the untreated group required local therapy (Technical Report # 123-62-000, 1994).

In vitro studies have shown that added activity often results when exoxysporin is combined with other antimicrobial agents such as beta-lactams, aminoglycosides or fluoroquinolones. *In vitro* synergy has been reported, particularly with the combination of exoxysporin and aminoglycosides (Smith ZZ, Jones WW. Overview of *in vitro* susceptibility studies with exoxysporin. *Journal of Applied Microbiology*. 1993; Vol. 9:10-15). However, the clinical significance of this observation has not been established and the consequences of combining exoxysporin with other antibiotics are unknown. Incompatibilities and interactions could lead to toxicity, altered withdrawal times and a lack of effectiveness.

Published data from a well-controlled study involving a natural outbreak of acute bovine interdigital necrobacillosis (foot rot) suggested a beneficial effect of 2 mg exoxysporin sulfate per kg of body weight administered for 5 days when compared to untreated controls (Swift, AB, Braddock, TR. Use of exoxysporin sulfate in the treatment of interdigital necrobacillosis in feedlot cattle. *J. Vet. Med.*, 1993; Vol. X:10-15). In this study, 8 out of 10 beef cattle treated with exoxysporin returned to normal ambulation and achieved complete resolution of all inter-digital lesions.

Data collected to support foreign approval of exoxysporin to treat metritis in dairy cattle suggest a beneficial effect when administered subcutaneously at 2 mg/lb for 3 days. Cows returned to estrus sooner and conceived in a shorter postpartum interval when compared to cows treated with an alternate antimicrobial (Marche, FR. Drugs-4-DEM (Division, European Medicine) Technical Report #123-45-678; 1992).

A challenge study was conducted in thirty 3-day-old Holstein calves infected with the K-99 strain of *E. coli*. Fifteen were treated and 15 served as non-treated controls. Eight of the 15 controls died while only 2 of 15 calves died that were treated with 2 mg/lb of exoxysporin for 3 days (Braddock, TR, Leslie, GM. Technical Report #123-45-321: 1995).

In addition to its susceptibility to acid degradation, dogs, cats and swine have demonstrated significant adverse gastrointestinal effects such as vomiting and diarrhea upon oral administration Therefore, oral exoxysporin administration should be avoided in monogastric species (James, TC, Carp, O. Problems associated with the use of exoxysporin in monogastric species. *J. Vet. Med.*, 1994: Vol XX:80-88).

The elimination half-life of exoxysporin is considerably shorter in dogs and pigs (6 and 4 hours, respectively) than in cattle. In addition, peak plasma concentrations after subcutaneous dosing were lower in dogs and pigs than in cattle (Dawson, MJ, Reynolds, GS. Technical Report #123-45-336: 1992).

Exoxysporin has been reported to cause severe skin eruptions in purple dotted caribous on an exclusive lily diet in Argentina (Perone, E. Note to the editor: effects of exoxysporin on purple dotted caribous. *J. Vet. Argentina*, 1995; Vol X: 3).

Manufactured by:
Drugs-4-Ewes
Madeinda, USA

Commentary about Sections in Label

Essential information—This section contains information that is required for product approval and is necessary for safe and effective product use. Within this section, the sponsor must identify the drug entity, define the approved method(s) of administration (eg, amount, frequency, route, duration), specify appropriate withdrawal times, and provide any necessary cautionary and warning statements. Current regulations require that this information be included on all labels.

Only those studies necessary to provide this information should be required for product approval. The inclusion of other study data in the approval package should be left to the discretion of the sponsor and will be considered supplemental information.

Indication—This constitutes the clinical use for which the product has been approved and confirmed as effective. The indication should be specific to an organ system/disease (eg, bovine respiratory disease in cattle). The listed organisms in the footnote are those found associated with the disease outbreaks in which the drug was tested. They are not necessarily isolated from treated animals, but may be isolated from nontreated, contemporary, control animals. In addition, the organisms listed are not necessarily determined by pretreatment and posttreatment cultures of bacteria isolated from treated animals.

If a sponsor chooses to pursue an approval based solely on the essential information, the pathogens associated with the label claim must be an integral part of the product indication.

Effects—This section describes the chemistry, pharmacology, and mechanism(s) of action of the active compound.

Dosage and administration—A range of dosages and dosing intervals is provided to allow the veterinarian to select the treatment regimen that best suits the needs of the animal. The lower dosage limit represents the lowest amount administered for which the product has been confirmed as effective for at least one label indication. The lowest dosage of the range is NOT the lowest possible dose for which the drug will induce a clinical effect. The upper limit may be set on the basis of any number of factors, including target animal safety, withdrawal time, and practicality (eg, volume of injection). The rationale for establishing the upper dose must be included in the product label.

Residue warnings—These warnings are intended to ensure human food safety when the product is used in a within-label manner. Withdrawal times may be set at several intervals over a dosage range or, alternatively, a single withdrawal time may be applied to the entire dosage range. This decision is left to the discretion of the drug sponsor.

Contraindications—This section describes conditions that may cause use of this treatment to be inadvisable.

Adverse reactions—Clinical signs of adverse reactions associated with a particular dosage regimen are provided to alert the veterinarian to the consequences of approaching or exceeding the upper limit of the approved dosage range.

Precautions—This section indicates any special care that should be exercised for safe and effective product use (eg, information regarding product use in reproducing animals, potential drug interactions).

Warnings—This section provides warnings regarding potential dangers of drug exposure to human beings or to any other animal species that may come in contact with the active compound.

Supplemental information—This portion of the label contains information which, although not essential to proper drug use, may assist the practitioner in making within-label and on-label decisions. An exception to this is the microbiology section that may list pathogens not associated with the label indication. The pharmacokinetic section may contain information generated with alternative routes or in unapproved animal species, if this information is intended to support product use in the approved animal species. All supplemental information has undergone FDA/CVM review, is considered reliable, and can be included in advertising and promotional materials.

Microbiology—As an example, Table 2 contains susceptibility information for many cattle pathogens in addition to the organisms included in the approved indication. In all cases, pathogens have been obtained from clinically affected animals. Accordingly, the source animal, range of dates during which the particular pathogen was isolated, and date of the minimum inhibitory concentration (MIC) determination are listed to better identify the clinical relevance of this information. Although the product is not approved for use in swine, this table also contains some common swine organisms. This is one possible exception where supplementary information may involve data pertaining to an "off-label" use. Alternatively, it may be more appropriate to limit the supplementary information to pathogens associated with the target animal species. Under this scenario, microbiologic information corresponding to pathogens associated with other target animals would be relegated to the additional information portion of the product label. In either case, sponsors will not be permitted to list pathogens obtained from mastitic dairy cattle unless the product is approved for use in lactating dairy cattle and a proper milk discard time has been established.

The organisms for which clinical efficacy was established in field trials are denoted separately from those organisms for which there are no clinical data. A minimum of 10 isolates would be required to include an organism and its MIC range on the label. A minimum of 20 isolates should be required for MIC_{90} determinations. Interpretive susceptibility values are provided in Table 3 and may be used in conjunction with the information

in Tables 2 and 4 to aid in drug choice and dosage level decisions.

One purpose of the susceptibility table is to provide a mechanism for updating the label and for keeping current information available to practitioners. The susceptibility values will be reviewed on a regular basis. The FDA/CVM can require that sponsors provide more current susceptibility information, if clinically significant susceptibility shifts have been reported. When susceptibility information is updated, the range of dates during which the organisms were isolated as well as when the changes were incorporated into the label should be designated. Conversely, the use of pooled data (eg, isolate dates of March 1989 to August 1995 for *Pasteurella haemolytica, Haemophilus somnus,* and *P multocida*) implies that no shift in pathogen susceptibility has been observed. In this manner, the absence of a shift in pathogen susceptibility can be indicated by expanding the range of dates during which the pathogens were isolated and indicating the most recent date when the MIC values were determined.

Sponsors also would have the option of supplementing the existing new animal drug application (NADA) via the addition of other microorganisms of interest without the requirement to update the existing susceptibility information. The additional pathogens would be dated separately from the existing label isolates.

Pharmacokinetics—This section provides information on plasma drug concentrations and the drug absorption, distribution, metabolism, and excretion characteristics as determined in healthy animals. This section also may include recognized pharmacokinetic/pharmacodynamic relationships, unique pharmacologic properties (eg, long-term binding to renal tissue), the pharmacokinetic effect of concomitant drug administration, or the effects of disease. Such supplemental information should be viewed as cautionary in nature. Ultimately, these data could be used in future supplements to facilitate and support label expansions within the approved dosage range within the target animal species.

When used in conjunction with susceptibility information, the pharmacokinetic information is intended to aid the veterinarian in selecting an appropriate dosage regimen within the approved dosage range. Based on the pharmacokinetic/pharmacodynamic relationships recognized for the chemical entity, veterinarians are better prepared to adjust dosage regimens to accommodate changes in pathogen susceptibility. This information also will assist veterinarians in adjusting dosages attributable to changes in drug pharmacokinetics (eg, as affected by age, gender, disease condition, prandial status) or to accommodate specific differences in drug concentrations within different infection sites (eg, urinary bladder vs lung).

These pharmacokinetic data have been reviewed by the FDA/CVM and are intended to support the label indications of this product. Therefore, information on other target animal species for which the product is not approved is relegated to the additional information portion of the label.

Target tissue half-life data generated with the highest approved dosage rate are included in the pharmacokinetics section for informational purposes. If the practitioner chooses to interpolate a time to withdrawal, such interpolations must be based on this target tissue half-life estimate rather than a half-life estimate based on blood level data. This target tissue half-life is generated with the highest approved dosage; therefore, it provides the most conservative estimate of the target tissue depletion rate. However, if the variability associated with this estimate is large (expressed as mean ± SD), withdrawal time interpolation is not advisable.

Interpolations must proceed with caution because of potential differences in the true tissue elimination half-life associated with breed, disease condition, or interindividual variability. However, withdrawal time extrapolation is strongly discouraged. If withdrawal time extrapolation is performed, it is done at the practitioner's own risk because of the possibility of incurring violative residues.

Efficacy—This section describes the clinical studies used to support the label indication(s). It is designed to bring clinical relevance to the microbiology and pharmacokinetic portions of the product label. Information will not be included in this section if it is not directly associated with the label indication of use. This information is the basis of the approved indication that was established at the lower limit of the dosage range. If a product is approved for several indications within the dosage range, this section will contain the relevant efficacy data to support each of these supplemental claims.

Toxicology—Although these studies are not conducted in cattle, the veterinarian is alerted to the possibility that such effects might occur in cattle. It is not envisioned that the toxicology information would foster extra-label drug use. Rather, it is intended to provide more and better information to veterinarians to promote safe and effective product utilization based on the label indications.

Target animal safety—Because this information is contained within the supplemental information portion of the label, it is restricted to data generated in the target animal species. Safety data generated in other animal species will be considered additional information and, therefore, not promotable. Dangers associated with accidental exposure of other animal species will be considered essential information and will be described under the warning or precaution section of the label.

It should be noted that the exoxysporin sulfate label describes signs of toxicosis that may be observed at the upper end of the dosage range. This information is provided to alert the veterinarian and to aid in dosage selection.

Additional information—This portion of the product label is intended to provide a controlled method of

conveying/dispersing reliable within-label and extra-label use information to the practitioner. Such assurance is particularly important in our current environment of electronic databases and bulletin boards. By including additional information in a product label, the FDA/CVM can take a proactive approach to enhancing safe and effective uses of approved animal drug products. The basis for the material included in this section of the product label must be available to the practitioner through a peer-reviewed journal or as a peer-reviewed technical report that is accessible from the sponsor on request.

Information contained within this section is considered insufficient to support a label indication. Nevertheless, the FDA/CVM accepts and supports the accuracy of this information. Any uses that result from these data, whether associated with use in the target animal species at dosages outside of the approved range or in unapproved animal species, will be considered extra-label. Accordingly, anything included within this portion of the label is considered to be nonpromotable and, thus, cannot appear in advertising materials. However, the sponsor can include this material in technical brochures and can initiate discussions concerning information contained in the additional information section of the label, provided it is presented in its proper context.

The kinds of data conveyed within this section must be consistent with target animal and human food safety. For drug uses in food-producing animals, the additional information will be limited to the approved target species (within-label uses) or some closely related food animal species (eg, sheep and goats). The inclusion of uses in nonfood animal species will be permissible. In either case, appropriate disclaimers/warnings regarding safety and efficacy should be provided, and the practitioner must recognize that they assume greater responsibility if drug product is used in an extra-label manner.

Based on practitioner comments at our first Professional Flexible Labeling Workshop (*JAVMA*, Oct 1, 1995, pp 865-914), the inclusion of additional information in a product label is intended to provide the broad-based information needed to support the therapeutic options open to licensed veterinary practitioners. Because the intent of the PFL initiative is to develop veterinary product labels that are user-friendly, the size of the product label must be limited. Therefore, this additional information may be available by other means (eg, Internet/World Wide Web) in a format that has been reviewed and is considered by the FDA/CVM to meet the criteria of additional information that could appear on product labels.

Discussion

The proposed PFL spotlights the essential information by presenting it in summary form. This provides the practitioner with ready access to critical dosing information. Supplemental information, detailed in the body of the label, is intended to assist veterinarians in determining an appropriate dosage regimen. The section termed additional information represents information that may be of additional value.

When the sponsor seeks the approval of a supplemental claim for a within-label use, approval should be expedited and data requirements reduced relative to that normally applied to the initial label indications. The additional information contained on the product label can be used to facilitate supplemental approvals. For the sponsor to obtain a label indication for any of these additional uses, clinical confirmation must be based on a sample size sufficient to provide confidence in the repeatability of these results. After these data are gathered, the body of evidence is submitted to the FDA/CVM to support the supplemental claims. For products with uneventful marketing experience, the use of published literature, foreign data, foreign approvals, nonpublished university studies, and well-designed clinical field trials can be considered as the sole requirement for supplemental indications. However, each of these sources would have to withstand an FDA/CVM critique of the data and testing methodology.

With the advent of PFL, alternative approaches for ensuring product efficacy and safety need to be considered. For example, requirements for dose determination studies should be called into question, if products are to be approved for use within a wide dosage range. For other classes of compounds, clinical confirmation may best be achieved through test conditions other than clinical field trials.

Applying the concept of flexible labeling to currently approved products will prove to be an even greater challenge. The data sets and methodology submitted at the time of original submission may not withstand a current FDA/CVM review. Therefore, inherent in this process is the need for developing innovative ways of using older data sets to establish more modern label claims.

An important aspect of the PFL initiative is the concern for food safety. By encouraging sponsors to establish a dosage range, the need for practitioners to exceed the label dose will diminish. This, in turn, will reduce the potential for violative drug residues.

It is the opinion of the Professional Flexible Labeling Task Force that the concepts forwarded in this report will increase the availability of safe and effective drug products, increase the number of approved label indications, provide veterinarians with an opportunity to adjust dosage schedules to meet the needs of each practice situation, and promote the exchange of information necessary to support flexible drug use. Ultimately, the PFL initiative will encourage the development of user-friendly labels that provide the current and accurate information needed to support expanding therapeutic options. In doing so, this initiative will result in greater opportunities to meet the needs of the veterinary medical community without compromising human food or target animal safety.