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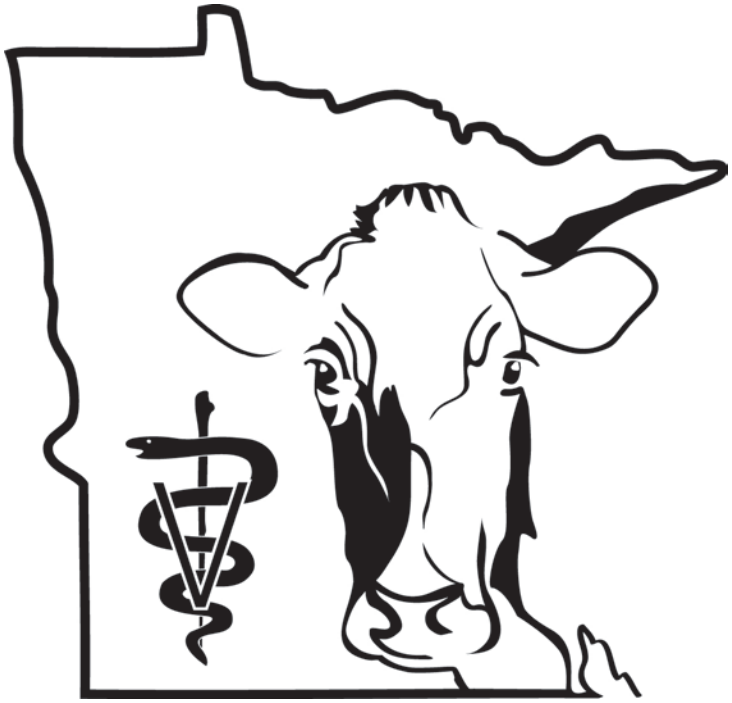

ST. PAUL, MINNESOTA
UNITED STATES OF MINNESOTA

Antimicrobial Clinical Pharmacology

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May 21, 1997
St. Paul, Minnesota

Handout:

Preparing for the world of flexible-labeling

"Science is merely an extension of common sense" - Einstein

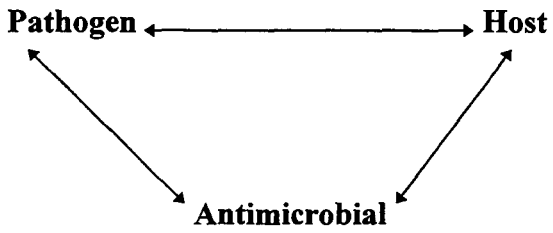
The philosophy of rational antimicrobial use:

Each of the antimicrobials we work with has a characteristic way of moving through the body. **Pharmacokinetics**

Each of the antimicrobials we work with has a characteristic way of interacting with a certain subset of microbes and the physiology of the host. **Pharmacodynamics**
Too often, antimicrobial therapy is viewed in this manner.

Antimicrobial ⟷ Pathogen

Remember: The host-pathogen interaction is as, or more important than the antimicrobial-pathogen interaction. When we use an antimicrobial, we are trying to alter the balance of this relationship in favor of the host.



Practical Pharmacokinetics:

Terms describing or making inferences about concentrations

Cmax is the highest concentration reached in the plasma or a specific tissue.

The **volume of distribution (Vd)** may be used as an indication of the relationship between vascular and extravascular concentrations for a drug. The apparent volume of distribution is the volume of fluid (expressed as l/kg of body weight) necessary to contain the total amount of drug in the body if it were uniformly distributed and the concentration in this hypothetical fluid were equal to the plasma concentration. Drugs that tend to stay in the plasma have a Vd much less than 1, drugs that have wide distribution have a Vd near 1, and drugs with very wide distribution have a Vd much greater than 1.

Area under the curve (AUC) refers to the total area under the plasma concentration curve. The AUC following an IV injection of a drug essentially represents "all of the drug". Comparing this AUC to the AUC following IM, SC, or oral administration allows the calculation of bioavailability. Bioavailability is the percent of a drug available after administration by a specified route (other than IV) compared to IV administration of the same amount.

Terms describing rates

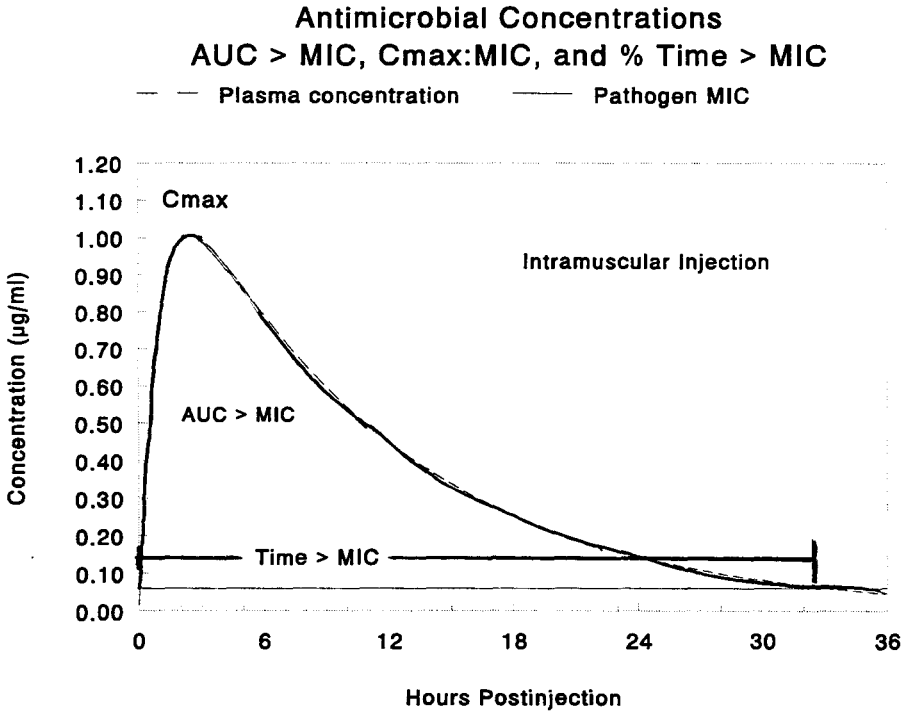
Tmax describes time to peak concentration in the plasma, this may also be described for a tissue. In the plasma, it is at the time of injection for an IV bolus, and reflects the rate of absorption from an IM injection.

T½α is the time required for the plasma concentration to decrease by ½ during the distribution phase of the plasma concentration curve (**distribution half-time**), and estimates the rate of distribution to the tissues. This phase consists primarily of distribution to the tissues, but also includes some elimination processes. It is greatly confounded by absorption following an IM injection.

T½β is the time required for the plasma concentration to decrease by ½ during the elimination phase of the plasma concentration curve (**elimination half-time**). Elimination from the plasma and tissues predominates in this phase. Although the plasma **T½β** may give an indication of the tissue **T½β**, they are not necessarily equal.

Summary

Rate of absorption - **Tmax**	Rate of distribution - **T½α**
Rate of elimination - **T½β**	Extent of absorption - **AUC**
Extent of distribution - **Vd**	



Caveat: You should have reservations any time a hard number is given for a pharmacokinetic (PK) parameter. Cmax, Tmax, and $T_{½\beta}$ will vary between animals within a species, and even between different administrations in the same animal, and that's in healthy animals! Almost all of the pharmacokinetic parameters reported for animal and human drugs are determined in healthy subjects.

Always view PK parameters reported as a single value as middle values in a range. For example, a study determining the elimination half-time of IV oxytetracycline in cattle found a mean of 9.04 hours, with a range of 6.97 to 10.98 hours. The introduction of disease variation would be expected to make the range even wider.

Take home point: Published PK parameters may be used as a rough starting point for the animal(s) you are working on. We should not consider published PK values as an accurate indication for individual cases when used in conjunction with pathogen susceptibility data. These PK values may be used as a base for ruling out drugs which are way out of a reasonable efficacy range for your case. Published PK data and pathogen MIC data are suitable for determining a rough starting point for individual cases.

Plasma concentrations vs. concentrations in specific tissues: Life would be relatively easy if all infections were combined to the vascular system. We have a good handle on drug concentrations and 'kinetics in the bloodstream. In contrast, the only people who truly understand tissue concentrations work in corporate marketing departments.

Tissue concentrations are usually determined by the tissue homogenization. A sample of tissue is taken, ground up, weighed, and then the drug is extracted from the sample and quantitated. The results are a μg/g concentration of drug. Water soluble agents (aminoglycosides, β-lactams, sulfas) are unable to penetrate parenchymal and immune cells, so their concentration in extracellular fluid is spread over the entire tissue mass by this method, falsely lowering the apparent concentration in the extracellular fluid. In contrast, lipid soluble agents (macrolides, fluoroquinolones, florfenicol) are concentrated in leukocytes. Again, their concentrations are averaged over all of the tissue, giving a falsely elevated impression of their concentration in extracellular fluid. (There is evidence that these compounds stay active in the leukocytes.) So how do we address this?

Water soluble compounds: It is usually accepted that the concentration of these compounds in extracellular fluid approximates the intravascular concentration. A water soluble compound is not usually the drug of choice for intracellular or facultative intracellular agents. Discussing "tissue penetration" will get you stepped on in some circles, yet it is reasonable to expect decreased presence of water soluble agents in extremely consolidated lung tissue where movement is required through tissue with an increased cellular content. It is well documented that water soluble agents typically have poor penetration into the prostate, CNS, and eye.

Lipid soluble compounds: These compounds tend to move through tissue rapidly and achieve very high tissue concentrations as we currently measure them. Comparing tissue homogenization derived concentrations directly to MICs to gauge potential efficacy is not accurate. It may be the case that these agents are actually concentrated where they will do the most good. However, do not assume the concentration in extracellular fluid is equal to the ""tissue concentration". A lipid soluble compound would be preferable for intracellular pathogens.

High lipid solubility: macrolides, fluoroquinolones, CHPC, florfenicol
Intermediate lipid solubility: tetracyclines,
Low lipid solubility: aminoglycosides, β-lactams, sulfas

Practical pharmacodynamics: Interactions between antimicrobials and pathogens

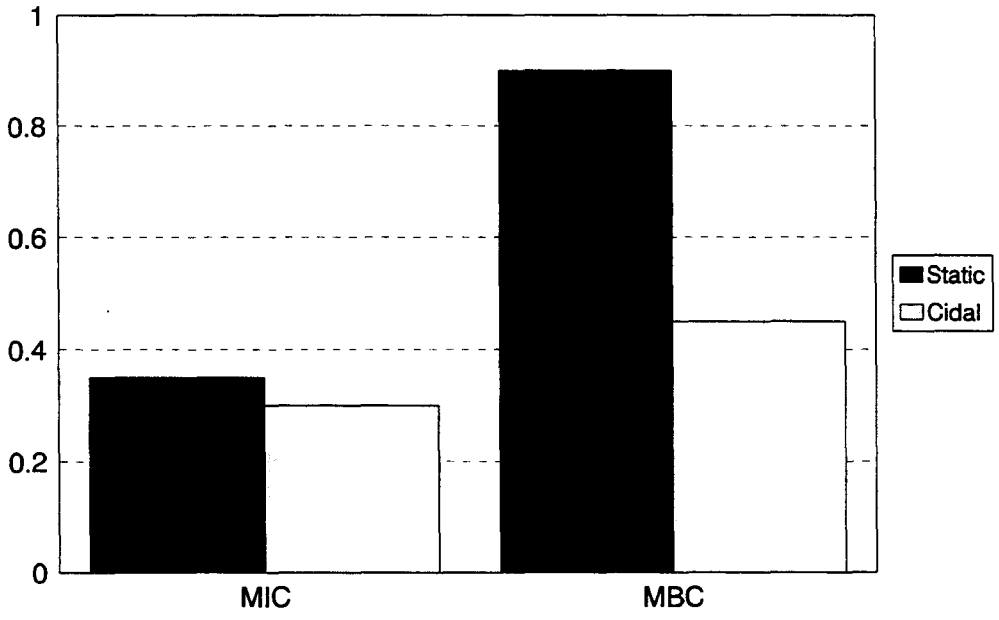
What is the most basic thing to know about an antimicrobial? How it kills microbes! Application of pharmacokinetics is futile without a knowledge of pharmacodynamics. A basic knowledge of bacteriostatic and bactericidal classifications along with site of action is a start.

Site of action:

Ribosome - 30S subunit*	Tetracyclines. Aminoglycosides, Aminocyclitols
Ribosome - 50S subunit*	Macrolides, Lincosamides, Florfenicol
Cell wall	β-lactams (Penicillins and Cephalosporins)
Purine synthesis	Sulfonamides, Trimethoprim
DNA gyrase inhibition	Fluoroquinolones

*Protein synthesis inhibitors

Bactericidal vs. Bacteriostatic: A range of pharmacodynamic interactions, not a hard and fast classification. This classification is based on the relationship between the MBC and the MIC.



Y axis = Concentration in μg/ml.
MIC = Minimal Inhibitory concentration
(inhibits all visible growth in culture for 18-24 hours)
MBC = Minimal Bactericidal Concentration (Kills all bacteria in culture)

Bacteriostatic	Bactericidal
Tetracyclines	β-lactams
Aminocyclitols	Aminoglycosides
Macrolides	Fluoroquinolones
Sulfonamides	
Florfenicol?	
Lincosamides	

The next step is to classify the antimicrobials as to the type of dosing regimen required for maximum efficacy.

Bacteriostatic antimicrobials and β-lactams require a substantial portion of the dosing interval above the MIC of the pathogen (usually relating to the plasma concentration). How long is a substantial portion? An educated guess would be 60-80% of the dosing interval, shorter end for gram (+) and longer end for gram (-) with β-lactams. It is interesting to see the bactericidal β-lactams in this group. It is thought this is because the cell wall of the bacteria become saturated with the β-lactam and increased concentrations do not help. In-vitro pharmacokinetic modeling with some pathogens has supported this theory. Increasing the in-vitro concentration of a β-lactam more than about 4x the MIC (in-vitro) does little to increase efficacy.

Fluoroquinolones and aminoglycosides are considered to be concentration-dependent, bactericidal antimicrobials. They respond favorably to increasing concentrations with little positive response to extended duration of drug concentrations. Some studies suggest that AUC may be the best predictor of fluoroquinolone efficacy, but remember that cranking the Cmax also has a pronounced effect on AUC. Fluoroquinolones are sometimes thought of as responding to "total exposure" of the pathogen to the antimicrobial. Published work in humans has suggested that a fluoroquinolone peak plasma concentration of at least 8-10x the pathogen MIC is required to prevent resistance in refractive pathogens such as *Pseudomonas*.

Getting a handle on drug/bug interactions: Interpretation of in-vitro susceptibility profiles:

There are two primary methods for bacterial susceptibility profile determination in use today.

1) Kirby-Bauer ("disk diffusion"): A paper disk containing the antimicrobial is placed on an agar plate that has been inoculated with the pathogen. The plate is incubated and the zones of inhibition (absent of any visible bacterial growth) are measured surrounding the disks. The diameter of the zone is proportional to the concentration of the antimicrobial at the point where bacterial growth is observed to start. The antimicrobial concentration just inside the edge of the inhibition zone is the Minimal Inhibitory Concentration. The diameter of the zone may be correlated to

serum/plasma concentrations obtainable in the animal and used to arrive at sensitive, intermediate sensitivity, or resistant classifications. This technique is obviously heavily dependent on quality control. Depth and contents of the agar, and antimicrobial contents of the disks must be closely controlled.

2) Sensititer® system (Breakpoint MICs): This system uses a plate with wells that contain different concentrations of the selected antimicrobials. Ideally we would have a well for each antimicrobial at 1:2 dilution intervals to accurately evaluate the MIC of the compound for each pathogen. However, cost prohibits this technique, so "breakpoints" are selected based on reported serum/plasma pharmacokinetic properties of antimicrobials in the species of interest. For example, commonly used breakpoints for tetracycline with bovine respiratory pathogens are 4 and 8 μg/ml.

   - A pathogen growing in neither of the wells would be considered susceptible
   - A pathogen growing only in the 4 μg/ml well would be considered intermediately susceptible
   - A pathogen growing in both wells would be considered resistant

My "sensitivity" interpretation guidelines:

1) Susceptibility patterns from a single case extrapolated to an entire production unit can be misleading, both as to the pathogen(s) involved and the susceptibility profile of the isolate. Repeated profiles should be coupled with observations of clinical response to evaluate your drug therapy. (Would you rely on an unpaired titer for a definitive diagnosis?)
2) Keep track of, and pay close attention to changes in susceptibility profiles from your cases, especially in different production units.
3) Place the most weight on susceptibility profiles from untreated animals. Be careful of extrapolating from nasal or nasal/pharyngeal swab results to what's going on in the lung.
4) Give more leeway on using antimicrobials to which the isolate is "moderately susceptible" in cases of bacteriostatic antimicrobials in animals that are expected to have competent immune systems. If you feel you need a bactericidal drug (I'm unsure of the clear-cut advantage vs. an efficacious bacteriostatic drug) in immunosuppressed cattle, then it is probably wise to select for a routinely "susceptible" compound.
5) Keep in mind that some compounds are placed in their absolute best light in susceptibility testing. Aminoglycosides are inactivated by low pH, low oxygen tension, and tend to bind to cellular debris. Sulfas work poorly in environments with pus.

This section contains the text of the final rule for extralabel drug use in animals. It was copied directly from the CVM homepage at http://www.cvm.fda.gov/. Copies may be obtained from this source or by contacting: Communications Staff, FDA-CVM, 7500 Standish Place, HFV-12, Rockville, MD 20855, (301) 594-1755.

Federal Register: November 7, 1996 (Volume 61, Number 217)]
[Rules and Regulations]
[Page 57731-57746]
From the Federal Register Online via GPO Access [wais.access.gpo.gov]

[[Page 57731]]

Part II

Department of Health and Human Services

Food and Drug Administration

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21 CFR Part 530

Extralabel Drug Use in Animals; Final Rule

[[Page 57732]]

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 530

[Docket No. 96N-0081]
RIN 0910-AA47

Extralabel Drug Use in Animals

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing a final rule to allow veterinarians to prescribe extralabel uses of certain approved animal drugs and approved human drugs for animals. This action implements the Animal Medicinal Drug Use Clarification Act of 1994 (the AMDUCA). This rule will provide veterinarians greater flexibility for using approved drugs for animal use.

DATES: This final rule is effective December 9, 1996.

FOR FURTHER INFORMATION CONTACT: Richard L. Arkin, Center for Veterinary Medicine (HFV-238), Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855, 301-594-1737.

SUPPLEMENTARY INFORMATION:

This section was deleted for the purposes of these proceedings. This section contains approximately 20 pages which cover background, summary of the proposed rule, discussion of comments received, comments on specific sections, effective dates, environmental impact, analysis of impacts, and other sections. The full text is available from the CVM homepage at http://www.cvm.fda.gov/ or by contacting: Communications Staff, FDA-CVM, 7500 Standish Place, HFV-12, Rockville, MD 20855, (301) 594-1755.

PART 530--EXTRALABEL DRUG USE IN ANIMALS

Subpart A--General Provisions

Sec.
530.1 Scope.
530.2 Purpose.
530.3 Definitions.
530.4 Advertising and promotion.
530.5 Veterinary records.

Subpart B--Rules and Provisions for Extralabel Uses of Drugs in Animals

530.10 Provision permitting extralabel use of animal drugs.
530.11 Limitations.
530.12 Labeling.
530.13 Extralabel use from compounding of approved new animal and approved human drugs.

Subpart C--Specific Provisions Relating to Extralabel Uses of Animal and Human Drugs in Food-Producing Animals
530.20 Conditions for permitted extralabel animal and human drug

use in food-producing animals.
530.21 Prohibitions for food-producing animals.
530.22 Safe levels and analytical methods for food-producing animals.
530.23 Procedure for setting and announcing safe levels.
530.24 Procedure for announcing analytical methods for drug residue quantification.
530.25 Orders prohibiting extralabel uses for drugs in food-producing animals.

Subpart D--Extralabel Use of Human and Animal Drugs in Animals Not Intended for Human Consumption

530.30 Extralabel drug use in nonfood animals.

Subpart E--Safe Levels for Extralabel Use of Drugs in Animals and Drugs Prohibited From Extralabel Use in Animals

530.40 Safe levels and availability of analytical methods.
530.41 Drugs prohibited for extralabel use in animals.

Authority: Secs. 4, 5, 6 of the Fair Packaging and Labeling Act (15 U.S.C. 1453, 1454, 1455); secs. 201, 301, 501, 502, 503, 505, 507, 512, 701, and 721 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 351, 352, 353, 355, 357, 360b, 371, 379e).

Subpart A--General Provisions

Sec. 530.1 Scope.

This part applies to the extralabel use in an animal of any approved new animal drug or approved new human drug by or on the lawful order of a licensed veterinarian within the context of a valid veterinary-client-patient relationship.

Sec. 530.2 Purpose.

The purpose of this part is to establish conditions for extralabel use or intended extralabel use in animals by or on the lawful order of licensed veterinarians of Food and Drug Administration approved new animal drugs and approved new human drugs. Such use is limited to treatment modalities when the health of an animal is threatened or suffering or death may result from failure to treat. This section implements the Animal Medicinal Drug Use Clarification Act of 1994 (the AMDUCA) (Pub. L. 103-396).

Sec. 530.3 Definitions.

(a) Extralabel use means actual use or intended use of a drug in an animal in a manner that is not in accordance with the approved labeling. This includes, but is not limited to, use in species not listed in the labeling, use for indications (disease or other conditions) not listed in the labeling, use at dosage levels, frequencies, or routes of administration other than those stated in the labeling, and deviation from the labeled withdrawal time based on these different uses.

(b) FDA means the U.S. Food and Drug Administration.

[[Page 57744]]

(c) The phrase a reasonable probability that a drug's use may present a risk to the public health means that FDA has reason to believe that use of a drug may be likely to cause a potential adverse event.

(d) The phrase use of a drug may present a risk to the public health means that FDA has information that indicates that use of a drug may cause an adverse event.

(e) The phrase use of a drug presents a risk to the public health means that FDA has evidence that demonstrates that the use of a drug has caused or likely will cause an adverse event.

(f) A residue means any compound present in edible tissues that results from the use of a drug, and includes the drug, its metabolites, and any other substance formed in or on food because of the drug's use.

(g) A safe level is a conservative estimate of a drug residue level in edible animal tissue derived from food safety data or other scientific information. Concentrations of residues in tissue below the safe level will not raise human food safety concerns. A safe level is not a safe concentration or a tolerance and does not indicate that an approval exists for the drug in that species or category of animal from which the food is derived.

(h) Veterinarian means a person licensed by a State or Territory to practice veterinary medicine.

(i) A valid veterinarian-client-patient relationship is one in which:

(1) A veterinarian has assumed the responsibility for making medical judgments regarding the health of (an) animal(s) and the need for medical treatment, and the client (the owner of the animal or animals or other caretaker) has agreed to follow the instructions of the veterinarian;

(2) There is sufficient knowledge of the animal(s) by the

veterinarian to initiate at least a general or preliminary diagnosis of the medical condition of the animal(s); and

(3) The practicing veterinarian is readily available for followup in case of adverse reactions or failure of the regimen of therapy. Such a relationship can exist only when the veterinarian has recently seen and is personally acquainted with the keeping and care of the animal(s) by virtue of examination of the animal(s), and/or by medically appropriate and timely visits to the premises where the animal(s) are kept.

Sec. 530.4 Advertising and promotion.

Nothing in this part shall be construed as permitting the advertising or promotion of extralabel uses in animals of approved new animal drugs or approved human drugs.

Sec. 530.5 Veterinary records.

(a) As a condition of extralabel use permitted under this part, to permit FDA to ascertain any extralabel use or intended extralabel use of drugs that the agency has determined may present a risk to the public health, veterinarians shall maintain the following records of extralabel uses. Such records shall be legible, documented in an accurate and timely manner, and be readily accessible to permit prompt retrieval of information. Such records shall be adequate to substantiate the identification of the animals and shall be maintained either as individual records or, in food animal practices, on a group, herd, flock, or per-client basis. Records shall be adequate to provide the following information:

(1) The established name of the drug and its active ingredient, or if formulated from more than one ingredient, the established name of each ingredient;

(2) The condition treated;

(3) The species of the treated animal(s);

(4) The dosage administered;

(5) The duration of treatment;

(6) The numbers of animals treated; and

(7) The specified withdrawal, withholding, or discard time(s), if applicable, for meat, milk, eggs, or any food which might be derived from any food animals treated.

(b) A veterinarian shall keep all required records for 2 years or as otherwise required by Federal or State law, whichever is greater.

(c) Any person who is in charge, control, or custody of such records shall, upon request of a person designated by FDA, permit such person designated by FDA to, at all reasonable times, have access to,

permit copying, and verify such records.

Subpart B--Rules and Provisions for Extralabel Uses of Drugs in Animals

Sec. 530.10 Provision permitting extralabel use of animal drugs.

An approved new animal drug or human drug intended to be used for an extralabel purpose in an animal is not unsafe under section 512 of the act and is exempt from the labeling requirements of section 502(f) of the act if such use is:

(a) By or on the lawful written or oral order of a licensed veterinarian within the context of a valid veterinarian-client-patient relationship; and

(b) In compliance with this part.

Sec. 530.11 Limitations.

In addition to uses which do not comply with the provision set forth in Sec. 530.10, the following specific extralabel uses are not permitted and result in the drug being deemed unsafe within the meaning of section 512 of the act:

(a) Extralabel use in an animal of an approved new animal drug or human drug by a lay person (except when under the supervision of a licensed veterinarian);

(b) Extralabel use of an approved new animal drug or human drug in or on an animal feed;

(c) Extralabel use resulting in any residue which may present a risk to the public health; and

(d) Extralabel use resulting in any residue above an established safe level, safe concentration or tolerance.

Sec. 530.12 Labeling.

Any human or animal drug prescribed and dispensed for extralabel use by a veterinarian or dispensed by a pharmacist on the order of a veterinarian shall bear or be accompanied by labeling information adequate to assure the safe and proper use of the product. Such information shall include the following:

(a) The name and address of the prescribing veterinarian. If the drug is dispensed by a pharmacy on the order of a veterinarian, the labeling shall include the name of the prescribing veterinarian and the name and address of the dispensing pharmacy, and may include the address of the prescribing veterinarian;

(b) The established name of the drug or, if formulated from more than one active ingredient, the established name of each ingredient;

(c) Any directions for use specified by the veterinarian, including the class/species or identification of the animal or herd, flock, pen, lot, or other group of animals being treated, in which the drug is intended to be used; the dosage, frequency, and route of administration; and the duration of therapy;

(d) Any cautionary statements; and

(e) The veterinarian's specified withdrawal, withholding, or discard time for meat, milk, eggs, or any other food which might be derived from the treated animal or animals.

Sec. 530.13 Extralabel use from compounding of approved new animal and approved human drugs.

(a) This part applies to compounding of a product from approved animal or human drugs by a veterinarian or a pharmacist on the order of a veterinarian within the practice of

[[Page 57745]]

veterinary medicine. Nothing in this part shall be construed as permitting compounding from bulk drugs.

(b) Extralabel use from compounding of approved new animal or human drugs is permitted if:

(1) All relevant portions of this part have been complied with;

(2) There is no approved new animal or approved new human drug that, when used as labeled or in conformity with criteria established in this part, will, in the available dosage form and concentration, appropriately treat the condition diagnosed. Compounding from a human drug for use in food-producing animals will not be permitted if an approved animal drug can be used for the compounding;

(3) The compounding is performed by a licensed pharmacist or veterinarian within the scope of a professional practice;

(4) Adequate procedures and processes are followed that ensure the safety and effectiveness of the compounded product;

(5) The scale of the compounding operation is commensurate with the established need for compounded products (e.g., similar to that of comparable practices); and

(6) All relevant State laws relating to the compounding of drugs for use in animals are followed.

(c) Guidance on the subject of compounding may be found in guidance documents issued by FDA.

Subpart C--Specific Provisions Relating to Extralabel Use of Animal and Human Drugs in Food-Producing Animals

Sec. 530.20 Conditions for permitted extralabel animal and human drug use in food-producing animals.

(a) The following conditions must be met for a permitted extralabel use in food-producing animals of approved new animal and human drugs:

(1) There is no approved new animal drug that is labeled for such use and that contains the same active ingredient which is in the required dosage form and concentration, except where a veterinarian finds, within the context of a valid veterinarian-client-patient relationship, that the approved new animal drug is clinically ineffective for its intended use.

(2) Prior to prescribing or dispensing an approved new animal or human drug for an extralabel use in food animals, the veterinarian must:

(i) Make a careful diagnosis and evaluation of the conditions for which the drug is to be used;

(ii) Establish a substantially extended withdrawal period prior to marketing of milk, meat, eggs, or other edible products supported by appropriate scientific information, if applicable;

(iii) Institute procedures to assure that the identity of the treated animal or animals is carefully maintained; and

(iv) Take appropriate measures to assure that assigned timeframes for withdrawal are met and no illegal drug residues occur in any food-producing animal subjected to extralabel treatment.

(b) The following additional conditions must be met for a permitted extralabel use of in food-producing animals an approved human drug, or of an animal drug approved only for use in animals not intended for human consumption:

(1) Such use must be accomplished in accordance with an appropriate medical rationale; and

(2) If scientific information on the human food safety aspect of the use of the drug in food-producing animals is not available, the veterinarian must take appropriate measures to assure that the animal and its food products will not enter the human food supply.

(c) Extralabel use of an approved human drug in a food-producing animal is not permitted under this part if an animal drug approved for use in food-producing animals can be used in an extralabel manner for the particular use.

Sec. 530.21 Prohibitions for food-producing animals.

(a) FDA may prohibit the extralabel use of an approved new animal or human drug or class of drugs in food-producing animals if FDA determines that:

(1) An acceptable analytical method needs to be established and

such method has not been established or cannot be established; or

(2) The extralabel use of the drug or class of drugs presents a risk to the public health.

(b) A prohibition may be a general ban on the extralabel use of the drug or class of drugs or may be limited to a specific species, indication, dosage form, route of administration, or combination of factors.

Sec. 530.22 Safe levels and analytical methods for food-producing animals.

(a) FDA may establish a safe level for extralabel use of an approved human drug or an approved new animal drug when the agency finds that there is a reasonable probability that an extralabel use may present a risk to the public health. FDA may:

(1) Establish a finite safe level based on residue and metabolism information from available sources;

(2) Establish a safe level based on the lowest level that can be measured by a practical analytical method; or

(3) Establish a safe level based on other appropriate scientific, technical, or regulatory criteria.

(b) FDA may require the development of an acceptable analytical method for the quantification of residues above any safe level established under this part. If FDA requires the development of such an acceptable analytical method, the agency will publish notice of that requirement in the Federal Register.

(c) The extralabel use of an animal drug or human drug that results in residues exceeding a safe level established under this part is an unsafe use of such drug.

(d) If the agency establishes a safe level for a particular species or category of animals and a tolerance or safe concentration is later established through an approval for that particular species or category of animals, for that species or category of animals, the safe level is superseded by the tolerance or safe concentration for that species or category of animals.

Sec. 530.23 Procedure for setting and announcing safe levels.

(a) FDA may issue an order establishing a safe level for a residue of an extralabel use of an approved human drug or an approved animal drug. The agency will publish in the Federal Register a notice of the order. The notice will include:

(1) A statement setting forth the agency's finding that there is a reasonable probability that extralabel use in animals of the human drug or animal drug may present a risk to the public health;

(2) A statement of the basis for that finding; and
(3) A request for public comments.
(b) A current listing of those drugs for which a safe level for extralabel drug use in food-producing animals has been established, the specific safe levels, and the availability, if any, of a specific analytical method or methods for drug residue detection will be codified in Sec. 530.40.

Sec. 530.24 Procedure for announcing analytical methods for drug residue quantification.

(a) FDA may issue an order announcing a specific analytical method or methods for the quantification of extralabel use drug residues above the safe levels established under Sec. 530.22 for extralabel use of an approved human drug or an approved animal drug. The agency will publish in the Federal Register a notice of the order, including the name of the specific analytical method or methods and the drug or drugs for which the method is applicable.

[[Page 57746]]

(b) Copies of analytical methods for the quantification of extralabel use drug residues above the safe levels established under Sec. 530.22 will be available upon request from the Communications and Education Branch (HFV-12), Division of Program Communication and Administrative Management, Center for Veterinary Medicine, 7500 Standish Pl., Rockville, MD 20855. When an analytical method for the detection of extralabel use drug residues above the safe levels established under Sec. 530.22 is developed, and that method is acceptable to the agency, FDA will incorporate that method by reference.

Sec. 530.25 Orders prohibiting extralabel uses for drugs in food-producing animals.

(a) FDA may issue an order prohibiting extralabel use of an approved new animal or human drug in food-producing animals if the agency finds, after providing an opportunity for public comment, that:
(1) An acceptable analytical method required under Sec. 530.22 has not been developed, submitted, and found to be acceptable by FDA or that such method cannot be established; or
(2) The extralabel use in animals presents a risk to the public health.
(b) After making a determination that the analytical method required under Sec. 530.22 has not been developed and submitted, or

that such method cannot be established, or that an extralabel use in animals of a particular human drug or animal drug presents a risk to the public health, FDA will publish in the Federal Register, with a 90-day delayed effective date, an order of prohibition for an extralabel use of a drug in food-producing animals. Such order shall state that an acceptable analytical method required under Sec. 530.22 has not been developed, submitted, and found to be acceptable by FDA; that such method cannot be established; or that the extralabel use in animals presents a risk to the public health; and shall:

(1) Specify the nature and extent of the order of prohibition and the reasons for the prohibition;

(2) Request public comments; and

(3) Provide a period of not less than 60 days for comments.

(c) The order of prohibition will become effective 90 days after date of publication of the order unless FDA publishes a notice in the Federal Register prior to that date, that revokes the order of prohibition, modifies it, or extends the period of public comment.

(d) The agency may publish an order of prohibition with a shorter comment period and/or delayed effective date than specified in paragraph (b) of this section in exceptional circumstances (e.g., where there is immediate risk to the public health), provided that the order of prohibition states that the comment period and/or effective date have been abbreviated because there are exceptional circumstances, and the order of prohibition sets forth the agency's rationale for taking such action.

(e) If FDA publishes a notice in the Federal Register modifying an order of prohibition, the agency will specify in the modified order of prohibition the nature and extent of the modified prohibition, the reasons for it, and the agency's response to any comments on the original order of prohibition.

(f) A current listing of drugs prohibited for extralabel use in animals will be codified in Sec. 530.41.

(g) After the submission of appropriate information (i.e., adequate data, an acceptable method, approval of a new animal drug application for the prohibited extralabel use, or information demonstrating that the prohibition was based on incorrect data), FDA may, by publication of an appropriate notice in the Federal Register, remove a drug from the list of human and animal drugs prohibited for extralabel use in animals, or may modify a prohibition.

(h) FDA may prohibit extralabel use of a drug in food-producing animals without establishing a safe level.

Subpart D--Extralabel Use of Human and Animal Drugs in Animals Not Intended for Human Consumption

Sec. 530.30 Extralabel drug use in nonfood animals.

(a) Because extralabel use of animal and human drugs in nonfood-producing animals does not ordinarily pose a threat to the public health, extralabel use of animal and human drugs is permitted in nonfood-producing animal practice except when the public health is threatened. In addition, the provisions of Sec. 530.20(a)(1) will apply to the use of an approved animal drug.

(b) If FDA determines that an extralabel drug use in animals not intended for human consumption presents a risk to the public health, the agency may publish in the Federal Register a notice prohibiting such use following the procedures in Sec. 530.25. The prohibited extralabel drug use will be codified in Sec. 530.41.

Subpart E--Safe Levels for Extralabel Use of Drugs in Animals and Drugs Prohibited From Extralabel Use in Animals

Sec. 530.40 Safe levels and availability of analytical methods.

(a) In accordance with Sec. 530.22, the following safe levels for extralabel use of an approved animal drug or human drug have been established: [Reserved]

(b) In accordance with Sec. 530.22, the following analytical methods have been accepted by FDA: [Reserved]

Sec. 530.41 Drugs prohibited for extralabel use in animals.

The following drugs are prohibited for extralabel animal and human drug uses in food-producing animals:

(a) Chloramphenicol;
(b) Clenbuterol;
(c) Diethylstilbestrol (DES);
(d) Dimetridazole;
(e) Ipronidazole;
(f) Other nitroimidazoles;
(g) Furazolidone (except for approved topical use);
(h) Nitrofurazone (except for approved topical use); and
(i) Sulfonamide drugs in lactating dairy cattle (except approved use of sulfadimethoxine, sulfabromomethazine and sulfaethoxypyridazine).

Dated: October 22, 1996.
William B. Schultz,
Deputy Commissioner for Policy.
[FR Doc. 96-28662 Filed 11-6-96; 8:45 am] BILLING CODE 4160-01-F

This section contains the text of the Animal Medicinal Drug Use Clarification Act and the compliance policy guide for compounding of drugs for use in animals. These were copied directly from the CVM homepage at http://www.cvm.fda.gov/. Copies may be obtained from this source or by contacting: Communications Staff, FDA-CVM, 7500 Standish Place, HFV-12, Rockville, MD 20855, (301) 594-1755.

FILE s340.enr

--S.340--

S.340

One Hundred Third Congress
of the
United States of America
AT THE SECOND SESSION
Begun and held at the City of Washington on Tuesday,
the twenty-fifth day of January, one thousand nine hundred and
ninety-four

An Act

To amend the Federal Food, Drug, and Cosmetic Act to clarify the application of the Act with respect to alternate uses of new animal drugs and new drugs intended for human use, and for other purposes.

[Italic->] Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled, [<-Italic]

SECTION 1. SHORT TITLE.

This Act may be cited as the `Animal Medicinal Drug Use Clarification Act of 1994'.

SEC. 2. UNAPPROVED USES.

(a) GENERAL RULE- Section 512(a) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360b(a)) is amended by adding the following new paragraphs at the end:

`(4)(A) Except as provided in subparagraph (B), if an approval of an application filed under subsection (b) is in effect with respect to a particular use or intended use of a new animal drug, the drug shall not be deemed unsafe for the purposes of paragraph (1) and shall be exempt from the requirements of section 502(f) with respect to a different use or intended use of the drug, other than a use in or on animal feed, if such use or intended use--

`(i) is by or on the lawful written or oral order of a licensed veterinarian within the context of a veterinarian-client-patient relationship, as defined by the Secretary; and

`(ii) is in compliance with regulations promulgated by the Secretary that establish the conditions for such different use or intended use.

The regulations promulgated by the Secretary under clause (ii) may prohibit particular uses of an animal drug and shall not permit such different use of an animal drug if the labeling of another animal drug that contains the same active ingredient and which is in the same dosage form and concentration provides for such different use.

`(B) If the Secretary finds that there is a reasonable probability that a use of an animal drug authorized under subparagraph (A) may present a risk to the public health, the Secretary may--

`(i) establish a safe level for a residue of an animal drug when it is used for such different use authorized by subparagraph (A); and

`(ii) require the development of a practical, analytical method for the detection of residues of such drug above the safe level established under clause (i).

The use of an animal drug that results in residues exceeding a safe level established under clause (i) shall be considered an unsafe use of such drug under paragraph (1). Safe levels may be established under clause (i) either by regulation or order.

`(C) The Secretary may by general regulation provide access to the records of veterinarians to ascertain any use or intended use authorized under subparagraph (A) that the Secretary has determined may present a risk to the public health.

`(D) If the Secretary finds, after affording an opportunity for public comment, that a use of an animal drug authorized under subparagraph (A) presents a risk to the public health or that an analytical method required under subparagraph (B) has not been developed and submitted to the Secretary, the Secretary may, by order, prohibit any such use.

`(5) If the approval of an application filed under section 505 is in effect, the drug under such application shall not be deemed unsafe for purposes of paragraph (1) and shall be exempt from the requirements of section 502(f) with respect to a use or intended use of the drug in animals if such use or intended use--

`(A) is by or on the lawful written or oral order of a licensed veterinarian within the context of a veterinarian-client-patient relationship, as defined by the Secretary; and

`(B) is in compliance with regulations promulgated by the Secretary that establish the conditions for the use or intended use of the drug in animals.'.

(b) OTHER AMENDMENTS-

(1) SECTION 301- Section 301 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 331) is amended--

(A) in paragraph (e), by striking `507(d) or (g),' and inserting `507(d) or (g), 512(a)(4)(C),'; and

(B) by adding at the end the following:

`(u) The failure to comply with any requirements of the provisions of, or any regulations or orders of the Secretary, under section 512(a)(4)(A), 512(a)(4)(D), or 512(a)(5).'.

(2) SECTION 512(e)- Section 512(e)(1)(A) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 360b(e)(1)(A)) is amended by inserting before the semicolon the following: `or the condition of use authorized under subsection (a)(4)(A)'.

(3) SECTION 512(l)- Section 512(l)(1) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360b(l)(1)) is amended by striking `relating to experience' and inserting `relating to experience, including experience with uses authorized under subsection (a)(4)(A),'.

(c) REGULATIONS- Not later than 2 years after the date of the enactment of this Act, the Secretary of Health and Human Services shall promulgate regulations to implement paragraphs (4)(A) and (5) of section 512(a) of the Federal Food, Drug, and Cosmetic Act (as amended by subsection (a)).

(d) EFFECTIVE DATE- The amendments made by this section shall take effect upon the adoption of the final regulations under subsection (c).

SEC. 3. MAPLE SYRUP.

(a) PREEMPTION- Section 403A(a) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 343-1(a)) is amended--

(1) in paragraph (1), by inserting at the end the following: `except that this paragraph does not apply to a standard of identity of a State or political subdivision of a State for maple syrup that is of the type required by sections 401 and 403(g),';

(2) in paragraph (2), by inserting at the end the following: `except that this paragraph does not apply to a requirement of a State or political subdivision of a State that is of the type required by section 403(c) and that is applicable to maple syrup,'; and

(3) in paragraph (3) by inserting at the end the following: `except that this paragraph does not apply to a requirement of a State or political subdivision of a State that is of the type required by section 403(h)(1) and that is applicable to maple syrup,'.

(b) PROCEDURE- Section 701(e)(1) (21 U.S.C. 371(e)(1)) is amended by striking `or maple syrup (regulated under section 168.140 of title 21, Code of Federal Regulations).'.

Speaker of the House of Representatives.

Vice President of the United States and

President of the Senate.

FDA CVM Home page

Sec.608.400

Compounding of Drugs for Use in Animals

COMPLIANCE POLICY GUIDE
CHAPTER - 6
SUB CHAPTER - 600
BACKGROUND:

The Federal Food, Drug, and Cosmetic Act (the Act) does not distinguish compounding from manufacturing or other processing of drugs for use in animals. However, veterinarians and pharmacists do manipulate drugs (e.g., combine or dilute finished dosage forms, prepare finished dosage forms from bulk drug substances, or prepare injectables from powdered oral dosage forms) to obtain products that differ from the starting materials.

There is a potential for causing harm to public health and to animals when drug products are compounded, distributed, and used in the absence of adequate and well-controlled safety and efficacy data, adherence to the principles of contemporary pharmaceutical chemistry and current good manufacturing practices.

The Agency acknowledges the use of compounding within certain areas of veterinary practice. The practice of veterinary medicine requires products to treat many conditions in a number of different species, some of which have unique physiological characteristics. FDA, other federal, state agencies, and producer groups encourage drug sponsors to obtain approvals for all new animal drugs.

While the Agency acknowledges the use of compounding under certain circumstances, it is also aware of adverse reactions and animal deaths caused by compounded drug products and is concerned about the risks associated with compounding practices in veterinary medicine. An example is the recent death of cattle due to the presence of endotoxin in a parenteral product prepared from spectinomycin approved for oral use. In addition, the Agency is greatly concerned about pharmacies that produce large quantities of unapproved new animal drugs that are essentially copies of FDA-approved products. These pharmacy products are actively advertised and promoted, and sometimes are priced lower than the approved product. The firms claim that they are practicing within the scope of their state licenses. However, it is apparent that some of these firms use their pharmacy licenses to circumvent the entire drug approval process, and are mass marketing products which have been produced with little or no quality control, manufacturing standards to ensure purity, potency and stability.

The pharmacokinetics and depletion times for residues from compounded products are not known and the assigning of extemporaneous withdrawal times may result in potentially harmful residues in food. Excipients and vehicles from unapproved or unknown origins may pose additional risks.

Section 510(g)(1) of the Act exempts from the registration requirements licensed pharmacies which do not compound drugs except exclusively within the regular course of their business of dispensing or selling drugs at retail. Section 510 (g)(2) exempts from the registration requirements licensed practitioners who manufacture, prepare, propagate, compound, or process drugs during the regular course of business of dispensing drugs at retail. The Act and regulations do not, however, exempt such practitioners or pharmacists from the approval requirements in the new animal drug provisions of Sections 501(a)(5) and 512. Therefore, compounding allowed under the Act is limited to the preparation of drug products which do not meet the definition of new animal drugs. In the absence of an approved new animal drug application (NADA), the compounding of a new animal drug from any article, including an approved or unapproved finished human or animal drug, or a bulk drug, results in an adulterated new animal drug in violation of section 501(a)(5).

Compounding from Approved Dosage Form Drugs: When the Animal Medicinal Drug Use Clarification Act of 1994 (AMDUCA) goes into effect, it will allow the "extra-label" use of approved animal and

human drugs. It will also allow compounding from those approved drugs. Under AMDUCA "extra-label" use, including compounding, will be subject to conditions specified by regulation. AMDUCA will become effective upon promulgation of the regulations. The scope of compounding made legal upon the effective date of AMDUCA will also be addressed by the regulations. The proposed regulations were published in the Federal Register on May 17, 1996. They have no effect until finalized.

Compounding from Bulk Drugs: Two Federal Appeals Court decisions, United States v. Algon Chemical Inc., 879 F.2d 1154 (3d Cir. 1989), United States v. 9/1 Kg. Containers, 854 F.2d 173 (7th Cir. 1988), affirmed the FDA position that the Act does not permit veterinarians to compound unapproved finished drug products from bulk drugs, unless the finished drug is not a new animal drug. The principle established by the court applies equally to compounding by pharmacists. However, one of the courts acknowledged the Agency's policy that, if the need is great and the risk small, the Agency may exercise regulatory discretion with respect to veterinarians compounding from approved drugs under Compliance Policy Guide (CPG) 615.100, Extra-label Use of New Animal Drugs in Food-Producing Animals.

DEFINITIONS:

The Act and accompanying regulations do not define compounding as different from other processing of drug compounds.

Bulk drug is an active ingredient (in unfinished form) intended for manufacture into finished dosage form drug products (from United States v. Algon Chemical Inc., 879 F.2d 1154 (3d Cir. 1989)). See also 21 CFR 207.3 (a) (4). Bulk drugs (or "bulk drug substances") may be supplied in various size containers and may or may not meet USP standards. Compounding is defined, for the purposes of this CPG, as any manipulation to produce a dosage form drug other than that manipulation that is provided for in the directions for use on the labeling of the approved drug product, for example, the reconstitution of a sterile powder with sterile water for injection.

Compounding ordinarily not subject to regulatory action, is defined as compounding by a licensed pharmacist or veterinary practitioner, when the criteria described in this document are met, within the confines of a legitimate practice. However, this document shall not be construed to bind the FDA or otherwise constrain its enforcement discretion. In addition, this document imposes no new obligations.

Compounding subject to regulatory action, is defined as compounding by a licensed pharmacist or other practitioner, when the criteria described in this document are not met, even if it is otherwise within the confines of a legitimate practice. Compounding outside the confines of a legitimate pharmacy or veterinary practice, whether by a pharmacist, veterinarian or other party, is subject to regulatory action.

"Legitimate practice" is defined as follows:

(a) Pharmacist: A person licensed and operating in conformity with state law, and dispensing in response to a valid prescription.

(b) Veterinarian: A person licensed and operating in conformity with state law, and prescribing or dispensing in response to a valid Veterinarian-Client-Patient Relationship (VCPR.)

Valid Veterinarian-Client-Patient Relationship (VCPR)

A valid VCPR exists when: (1) the veterinarian assumes the responsibility for making medical judgments regarding the health of the animal(s) and the need for medical treatment, and the client (owner or other caretaker) agrees to follow the instructions of the veterinarian; and (2) the veterinarian has sufficient knowledge of the circumstances to initiate at least a general or preliminary diagnosis of the medical condition of the animal(s), i.e., the veterinarian has recently seen and is personally acquainted with the keeping and care of the animal(s) by virtue of an examination of the animal(s), and/or by medically appropriate and timely visits to the premises where the animal(s) are kept; and (3) the practicing veterinarian is readily available for follow-up in case of adverse reactions or failure of the regimen of therapy. Source: American Veterinary Medical Association.

POLICY:

Circumstances exist when it may be necessary for a veterinarian to compound, or direct for a pharmacist to compound, an article that will result in an unapproved new animal drug. There is occasionally a need to utilize drugs labeled for human use, and much less commonly, bulk drug substances, for compounding into an appropriate dosage form. Some examples of these situations include: combinations of anesthetic drugs for titrated administration; preparation of dilute dosage forms for small, young, or exotic species patients; and usage of some antidote preparations. The Agency will exercise regulatory discretion and ordinarily would not take regulatory action against violations of the Act resulting from compounding an unapproved new animal drug if a determination is made that, in order to provide appropriate medical therapy, it is necessary to compound a new animal drug when the following conditions are met:

(1) A legitimate medical need is identified (the health of animals is threatened and suffering or death would result from failure to treat the affected animals),

(2) There is a need for an appropriate dosage regimen for the species, age, size, or medical condition of the patient,

and

(3) There is no marketed approved animal drug which, when used as labeled or in an "extra-label" manner in conformity with criteria listed in CPG 615.100, or human-label drug, when used in conformity with criteria listed in CPG 608.100, may treat the condition diagnosed in the available dosage form, or there is some other rare extenuating circumstance. (For example, the approved drug cannot be obtained in time to treat the animal(s) in a timely manner, or there is a medical need for different excipients.)

After making the above determinations, the following criteria should be met and precautions observed:

(1) Dispensing by a licensed veterinarian; or the receipt of a valid prescription of a licensed veterinarian by a pharmacist. Dispensing should be within the confines of a valid veterinarian-client-patient relationship. Veterinarians should exercise professional judgment to determine when compounding requires the services of a pharmacist. Professional assistance is appropriate when the complexity of compounding exceeds the veterinarian's knowledge, skill, facilities, or available equipment.

(2) The veterinarian takes measures to ensure that:

(a) When used in food-producing animals: no illegal residues occur; a significantly extended time period is assigned for drug withdrawal; and steps are taken to assure that the assigned time frames are observed;

(b) The safety and efficacy of the compounded new animal drug is consistent with current standards of pharmaceutical and pharmacological practices, e.g., known incompatibilities are avoided;

(c) Appropriate steps are taken to minimize risk of personnel exposure to potentially harmful ingredients in the preparation process; and

(d) Procedures are instituted to assure that appropriate patient records for the treated animals are maintained.

(3) All drugs dispensed to the animal owner by the veterinarian or a pharmacist, bear labeling information which is adequate to assure proper use of the product. The following label information should be included:

(a) Name and address of the veterinary practitioner;

(b) the active ingredient or ingredients;

(c) the date dispensed and the expiration date, which should not exceed the length of the prescribed treatment except in cases where the veterinarian can establish a rationale for a later expiration date;

(d) directions for use specified by the practitioner, including the class/species or identification of the animals; and the dosage, frequency, route of administration, and duration of therapy;

(e) cautionary statements specified by the veterinarian and/or pharmacist (this would include all appropriate warnings necessary to ensure safety of human operators handling the finished drug, especially if there are potential hazards of exposure to any components);

(f) the veterinarian's specified withdrawal/discard time(s) for meat, milk, eggs, or any food which might be derived from the treated animal(s) (while the veterinarian must set the withdrawal time, the veterinarian in doing so may use relevant information provided by a dispensing pharmacist although the veterinarian retains ultimate responsibility);

(g) if dispensed by a licensed pharmacist, the name and address of the dispenser, serial number and date of order or its filing;

(h) if dispensed by a veterinarian, the serial number; and

(i) any other applicable requirements of state or federal law.

(4) The pharmacist adheres to the National Association of Boards of Pharmacy Good Compounding Practices (GCP), or to equivalent state good compounding practice regulations, except where provisions conflict with this CPG. Among other practices, pharmacists should keep records of compounding formulas, logs of compounded items and specific ingredients, record of assurance of quality of raw materials; and information on adverse effects and product failures. Pharmacists should label compounded products with expiration dates that do not exceed the prescribed period of treatment, and with withdrawal times furnished by the prescribing veterinarian.

Veterinarians and pharmacists who compound or prescribe compounded medicaments and pharmacists who compound medicaments according to these guidelines criteria set out above would be considered to be engaged in extemporaneous compounding not ordinarily subject to regulatory action.

REGULATORY ACTION GUIDANCE:

Investigations will be conducted in coordination with state officials as specified in the October 26, 1995 letter from Associate Commissioner for Regulatory Affairs (FDA) and Executive Director, National Boards of Pharmacy, to state pharmacy and drug regulatory officials, and FDA officials.

FDA actions based on violative conditions will be consistent with state laws and regulations to the extent possible. Deviations from GCP may be deferred to state authorities for action. In general, the agency will place its highest regulatory priority on compounding products for use in food animals.

A. The following situations would likely indicate compounding subject to regulatory action and the existence of one or more would ordinarily be of high regulatory priority.

-Preparation for sale of large quantities of unapproved new animal drugs on an ongoing basis and where no valid medical need or VCPR exists. Compounding very limited quantities in anticipation of future need is acceptable provided that a history of past need can be documented;

-Compounding of medicaments that are essentially similar to FDA-approved products except in rare instances where a legitimate need can be established, for example, to treat animals on a timely basis or to avoid problems caused by certain excipients.

-Substitution or recommendation by a pharmacist of a compounded medicament for a prescription instead of using an FDA-approved product;

-Compounding from bulk drugs for use in food animals, with the rare exception of those medicaments that are permitted to be compounded by the Center for Veterinary Medicine (CVM) through compassionate regulatory discretion or other means (such as certain antidotes, large volume electrolyte products and other substances). Because these items may be revised, an official contact office at CVM has been designated to provide current information. That contact office is HFV-236, Case Guidance Branch, Division of Compliance, (301) 594-1785.

-Preparation for sale of unapproved new animal drugs on any scale which employ fanciful or trade names, colorings or other additives, or in any way imply that the products have some unique effectiveness or composition;

-Advertising, promotion, display, sale, or other means of marketing, prepared unapproved new animal drugs; and soliciting business to compound specific drug products, product classes or therapeutic classes of drug products;

-Offering compounded medicaments at wholesale to other state licensed veterinarians or pharmacists or other commercial entities for resale;

-Offering financial incentives such as rebates and consulting fees; and

-Dispensing of large quantities of compounded medicaments, where questions of stability of the finished product would arise;

-Failing to follow good compounding practices, including current standards of pharmaceutical and pharmacological practices, as described above;

-Labeling a product with an expiration date that exceeds the prescribed treatment period;

-Labeling a product with a withdrawal time established by the pharmacist instead of the veterinarian;

-Dispensing a disproportionate amount of compounded products out of state. The primary concern is the difficulty of maintaining proper relationships, for example, pharmacist/veterinarian/client and VCPR. Rare instances of specialized compounding to meet emergency needs would not be considered disproportionate.

B. The following situations would indicate excessive risk to public health or to animals, or an otherwise adverse risk/benefit ratio, of high regulatory priority:

-Instances where illegal residues occur in meat, milk, eggs, honey, or aquaculture products and the residues were caused by the use of a compounded drug in association with the violation being investigated;

-Compounding of medicaments for food-producing animals, especially those used in lactating dairy animals, which cause a significant risk of illegal residues because, for example, withholding times have not been established by the veterinarian using adequate scientific information; and

-Preparation of drug products that are essentially similar to products that have been removed from the market due to regulatory concerns, for example, chloramphenicol, dimetridazole, DES in food animals.

C. The following activities would indicate compounding subject to regulatory action, and possibly of high regulatory priority. However, guidance from CVM should be solicited to assess the potential public health threat and/or animal safety (i. e., risk vs benefits).

-Instances where animals have been harmed or their safety unnecessarily compromised, such as

compounding a nonsterile product for parenteral or ophthalmic administration where a sterile product is indicated, or other instances of not adhering to good compounding practices.

-Compounded substances that do not bear the required label information, including the name of the authorizing veterinarian, the active ingredients, directions for use, cautionary statements, and withdrawal times.

D. The following compounding situations would not ordinarily be considered for regulatory action. Appropriate state and local practice and pharmacy laws must be adhered to, however.

-Compounding for non-food animals and minor food animal uses where public health and animal safety have not been threatened, and are of great need and small risk. This would include such common practices as: veterinarians' combining agents for anesthesia, large volume parenterals, preparing appropriate dosage-forms for the size of the patient in question, "animal-side" compounding, and other similar common practices that are widely accepted in the day to day treatment of animal patients.

-Compounding from bulk drug substances for use in nonfood animals, including animals in public and private aquaria, when animal health is not threatened, and there is not a significant risk of diversion of the bulk drugs or compounded drugs for use in food animals. Bulk drug substances would ordinarily be expected to be in small packages that meet or exceed USP standards; see definition of "bulk drugs" above. Compounding should be performed in accordance with current standards of pharmaceutical practice (including referral to compendial monographs or established pharmacy textbooks).

If circumstances exist on a case-by-case basis that indicate otherwise, the Field should request guidance from CVM before considering regulatory action. The preceding is not intended to be a complete list of activities relating to compounding; there may be other factors which are appropriate when assessing an individual case.

GUIDANCE FOR CHARGING VIOLATIONS:

A warning letter is ordinarily the first choice of action, when referral to state authorities is not appropriate. Injunction would be the usual choice of court action, although seizure should be considered in the case of high priority drugs such as chloramphenicol or DES intended for use in food animals. Criminal action can be considered in egregious situations.

Compounded drugs subject to regulatory action under this policy will ordinarily be charged as unapproved new animal drugs, violative under Section 501(a)(5). Deviations from GCP, if not subject of state action will ordinarily be charged under Section 501(a)(2)(b). The tissue residue violations are covered under Section 402 (a) (2) (D).

Date: July 3, 1996, *Federal Register* Doc. 96-16973

Return to Compliance Policy Guidelines Table of Contents