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: Notice of proposed rulemaking.

SUMMARY: The Food and Drug Administration (FDA) is proposing 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 proposed rule will provide veterinarians greater flexibility for using approved drugs for animal use.

DATES: Written comments on the proposed rule by July 31, 1996. Written comments on the information collection requirements should be submitted by June 17, 1996.

ADDRESSES: Written comments on the proposed rule to the Dockets Management Branch (HFA–305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1–23, Rockville, MD 20857.

Submit written comments on the information collection requirements to the Office of Information and Regulatory Affairs, Office of Management and Budget (OMB), New Executive Office Building, 725 17th St. NW., rm. 10235, Washington, DC 20503, ATTN: Desk Officer for FDA.

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:

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I. Background

A. The Provisions of the AMDUCA

FDA is proposing rules to implement the AMDUCA (Pub. L. 103–396) which was signed into law on October 22, 1994. Prior to enactment of the AMDUCA, section 512 of the act (21 U.S.C. 360b) provided that a new animal drug (NAD) is deemed unsafe unless it is subject to an approved application and the drug, its labeling and its use conform to such approved application. Therefore, use of an NAD without an approved application or in a manner different from that set out in an approved application resulted in the drug being unsafe under the act. Section 501(a)(5) of the act (21 U.S.C. 351(a)(5)) provides that a drug deemed to be unsafe under section 512 is adulterated. The AMDUCA allows veterinarians to prescribe extralabel uses of approved animal drugs and approved human drugs for animals.

The provisions of the AMDUCA relating to extralabel use of approved NAD's provide that such use must be in accordance with conditions specified by the Secretary of Health and Human Services (the Secretary) by regulations. The animal drug provisions also include several safeguards in allowing veterinarians to prescribe drugs for extralabel uses: (1) If the Secretary finds there is a reasonable probability that an extralabel use may present a risk to public health, the Secretary may establish a safe level for a residue for such extralabel use by regulation or order, and may require the development of analytical methods for residue detection; (2) the Secretary may, by general regulation, provide access to records of veterinarians to ascertain any use or intended use that the Secretary determines may present a risk to public health; and (3) if the Secretary finds, after affording an opportunity for public comment, that an extralabel animal drug use presents a risk to public health or that no acceptable analytical method has been developed and submitted, the Secretary may prohibit such extralabel use by order. In addition, the AMDUCA provides that an extralabel use of an approved NAD is not permitted if the label of another animal drug with the same active ingredient, dosage form, and concentration provides for that different use.

The AMDUCA also allows veterinarians to prescribe approved human drugs for use in animals under conditions specified by the Secretary by regulations. The human drug provisions do not, however, contain the express conditions set out in the statute for extralabel use of approved NAD's.

The AMDUCA adds a new section 301(u) to the act (21 U.S.C. 331(u)) which provides that failure to comply with the regulations or orders implementing the AMDUCA is a prohibited act. In addition, the AMDUCA amends section 512(l) of the act to require drug sponsors to keep records and make reports regarding extralabel uses.

Neither the AMDUCA nor the implementing regulations are intended to lessen the responsibility of the manufacturer, the veterinarian, or the food producer with regard to violative drug residues or other adverse impact on human health. Under the act and this proposal, any amount of residue that may present a risk to public health resulting from an extralabel use would constitute a violation of the act subject to enforcement action, if a safe level or tolerance has not been established. Residue exceeding an established safe level would also constitute a violation of the act, as would residue resulting from an extralabel use where the residue exceeds an established tolerance.

The AMDUCA requires that the Secretary issue final rules implementing the statute within 2 years of the enactment date. The provisions of the AMDUCA are effective upon adoption of the final rules.

B. FDA's Extralabel Drug Use Policies

Under the current statute, extralabel use of drugs in animals is a violation of the act, therefore, FDA set out its enforcement policies regarding such use in two FDA Compliance Policy Guides (CPG's). The first of these was issued on March 9, 1984, as CPG 7125.06, ''Extralabel Use of New Animal Drugs in Food-Producing Animals,'' and was revised most recently on July 20, 1992. In March 1995, CPG 7125.06 was published as Section 615.100 of Chapter

6 in a new agency compilation of CPG's entitled the ''FDA Compliance Policy Guides Manual, first edition'' (Washington: Government Printing Office, publication 1995–386–982–3373, 1995). The second relevant CPG, ''Human-Labeled Drugs Distributed and Used in Animal Medicine,'' was issued as CPG 7125.35 on March 19, 1991, and was last revised on July 20, 1992. It has been published as Section 615.100 in Chapter 6 of the CPG Manual.

The extralabel CPG's were issued to provide information and direction to FDA personnel in the field about the circumstances in which FDA would take regulatory action against extralabel use of approved NAD's and human drugs in animals and the situation in which the agency would exercise its regulatory discretion and not take action. The scant legislative history of the AMDUCA includes some evidence that the AMDUCA is intended to codify policies similar to those in FDA's CPG's. While there are no committee reports on the AMDUCA, floor statements of individual members of Congress express this intent. For example, Senator Pressler said in debate on the bill, ''FDA has stated it will not institute regulatory action against licensed veterinarians for using or prescribing any drugs legally obtained. Thus, this bill codifies existing FDA practice.'' (140 Congressional Record S14072 (daily ed. October 4, 1994)). Senator Coats made a similar statement on the floor when he noted that the AMDUCA ''codifies the practices allowed under the current compliance policy guidelines'' regarding the extralabel use of veterinary pharmaceutical products. (140 Congressional Record S14272 (daily ed. October 5, 1994)).

Consistent with these congressional statements, FDA has generally followed policies similar to those in the existing CPG's in this proposed rule. For the public's convenience, the texts of the extralabel CPG's are included in this document in an appendix to the preamble. Itis anticipated that the CPG's will be withdrawn after a final rule based on this proposal has been published.

II. Description of the Proposed Rule

A. Scope and Purpose

The proposed rule would apply to the extralabel use in an animal of any approved NAD or approved human drug used by or on the lawful order of a veterinarian within the context of a veterinarian-client-patient relationship. Human drugs include approved new human drugs, as well as over-the-counter (OTC) drugs marketed under OTC monographs as safe and effective and not misbranded within the meaning of 21 CFR part 330. The proposal applies only to the extralabel use of approved NAD's and approved human drugs and not to the use of unapproved drugs.

Consistent with the policies in the CPG's, these proposed rules limit extralabel uses for food-producing animals to those that provide alternative treatment modalities when the health of an animal is threatened, or suffering or death may result from failure to treat an animal, i.e., therapeutic uses. FDA, however, has received increased requests to permit extralabel drug use for certain nontherapeutic uses such as uses related to enhanced animal reproduction. For example, representatives of the aquaculture industry have expressed a need for extralabel uses of drugs for spawning and gender reversal processes. Those representatives contended that certain aquaculture industries would not be able to survive economically without such extralabel uses, because approved drugs have not been available for those uses. Comments by members of the Veterinary Medicine Advisory Committee (VMAC) and others at the April 1995 VMAC meeting generally agreed that extralabel uses might be extended to some reproductive uses in terrestrial and, especially, aquatic animals.

The agency, in considering the appropriate scope of extralabel use under the statute, is concerned about the possible deterrent effect of such broad extralabel use on the widely-shared goal of increasing the number of approved drugs that are available for animal use. Therefore, the agency is interested in public comments as to nontherapeutic extralabel uses such as reproductive uses in terrestrial and, especially, aquatic animals and other possible uses. The agency also is interested in public comment as to appropriate ways to balance extralabel use with the need to preserve the goal of increased availability of new animal drugs approved for such uses under section 512 of the act.

B. Definitions

Proposed § 530.3 includes definitions of relevant terms. The term ''extralabel use'' means the actual or intended use of a human or animal 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 or for indications (disease or other therapeutic 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. Any deviation from labeled withdrawal time based on these different uses must be supported by appropriate scientific information.

The proposed rule defines the term ''residue'' to mean any compound present in edible animal tissues that results from the use of a drug, and would include the drug, its metabolites, and any other substance formed in or on food because of the drug's use.

The proposal defines a ''safe level'' as a conservative estimate of a drug residue level in animal tissue derived from toxicology and metabolism data or other scientific information. This level would be established so that concentrations of residues in tissue below the safe level will not raise human food safety concerns.

Under the proposal, a safe level would not be either a safe concentration or a tolerance and would not indicate that an approval exists for the drug in that species or category of animals from which the food is derived. If FDA establishes a safe level and a tolerance is later established through an approval for a particular species or category of animals, the safe level would be superseded by the tolerance for that species or category of animals, and would be revoked.

The term ''veterinarian'' is defined as a person licensed by a State or Territory to practice veterinary medicine, and who holds a degree of Doctor of Veterinary Medicine (D.V.M.), Veterinary Medical Doctor (V.M.D.), or the equivalent, from an accredited institution.

A ''valid veterinarian-client-patient relationship'' is defined as one in which: (1) A veterinarian has assumed the responsibility for making medical judgments regarding the health of an animal and the need for medical treatment, and the client (the owner or other caretaker of the animal or animals) 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 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. This definition is consistent with the American Veterinary Medicine

Association's definition of a ''valid veterinarian-client-patient relationship.''

The proposed rules, for purposes of establishing a safe level and requiring the development of analytical methods to detect residues, define the phrase *''a reasonable probability that a drug's use may present a risk to the public health''* as a circumstance in which FDA has reason to believe that use of a drug may be likely to cause a potential adverse event. The proposal, for purposes of providing access to veterinarians' records, would define the phrase *''use of a drug may present a risk to the public health''* to mean a circumstance in which FDA has information that indicates that use of a drug may cause an adverse event. In addition, under the proposal, the phrase *''use of a drug presents a risk to the public health,''* for purposes of prohibiting an extralabel use, means a circumstance in which FDA has evidence that demonstrates that the use of a drug has caused or is likely to cause an adverse event.

In defining these phrases regarding risk, the agency considered the common meaning of the words in these phrases, and other regulations in which FDA has defined similar concepts (e.g., 21 CFR 7.3(m), 7.41, and 803.3(r). The statute provides for an increased level of FDA activity as evidence of public concern becomes more substantial, and as the connection between specific extralabel uses and effect on the public health becomes more apparent. The final step may be prohibition of specified extralabel uses.

A finding that there is a reasonable probability that ''a drug's use may present a risk to the public health'' could be based on relevant information—assessed in the light of the education and experience of an agency staff member or other qualified person—that there may be a connection between a use and a potential adverse event. This would differ from a finding that ''use of a drug may present a risk to the public health,'' which would normally be based on some greater level of information that demonstrates that there may be some more concrete link between the use and an adverse event. In contrast, a finding that ''use of a drug presents a risk to the public health'' would require strong evidence of a direct link between the use and the risk.

FDA intends that harm that results from chronic low level or repeat exposure that is not high enough to cause acute toxicity but that could cause toxicity over long periods of time is included within the meaning of ''adverse event.''

C. Specific Issues

1. Extralabel Use When Approved Drugs are Available For Intended Therapeutic Purposes.

FDA's discretionary policies have precluded extralabel use of an animal or human drug in food-producing animals when an approved drug for the intended use exists. A similar limitation has not applied in the case of animal and human drugs used in animals not intended for human consumption; the agency has exercised broad enforcement discretion with regard to extralabel use in those species.

The AMDUCA provides that an extralabel use of an approved animal drug is not permitted if an approved NAD with the same active ingredient in the same dosage form and concentration exists for that use. The statute does not limit this provision to food-producing animals as FDA did in its CPG. Therefore, proposed § § 530.20(a)(1) and 530.30(a) limit the extralabel use of approved animal drugs in all animals to circumstances in which there is no approved NAD in the needed dosage form and concentration. The CPG contains an exception that permits an extralabel use where the veterinarian finds, within the context of a valid veterinarian-client-patient relationship, that an approved NAD is clinically ineffective for its intended use. The proposed rule does not include a similar provision. However, the agency invites comment as to whether the agency should permit such an exception.

The AMDUCA does not restrict extralabel use of approved human drugs in a similar manner. However, these proposed rules include the same limitation for extralabel use of human drugs in food-producing animals. FDA believes that, because of the broad public health implications inherent in the treatment of animals that will become food, it is prudent to require the use of an approved NAD if one exists before the extralabel use of a human drug is appropriate.

2. Compounding

FDA considers compounding from an approved drug to be an extralabel use. Thus, the agency views the language of the AMDUCA as giving statutory authorization to the compounding of finished drug products from approved human or approved animal drugs, within limits, under the same conditions as for any other extralabel use. FDA has certain concerns relative to compounding and the use of compounded drugs that can be distinguished from those issues associated with simple extralabel use of an approved finished drug product.

In view of the above, the proposed rule includes several major factors in addition to the general criteria set forth elsewhere in this proposed rule applicable to the extralabel use by compounding from approved drugs. The proposal provides that such extralabel use is permissible if: (1) All relevant portions of proposed part 530 have been complied with; (2) there is no marketed or approved human or new animal 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; (3) compounding is performed by a licensed pharmacist or veterinarian within the scope of a professional practice; (4) adequate processes and procedures are followed that ensure the safety and effectiveness of the compounded products; (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.

The AMDUCA does not authorize compounding from bulk drugs or unapproved drugs. Compounding by or for veterinarians from bulk drugs or unapproved drugs results in the production of an unapproved NAD that may be subject to regulatory action. Accordingly, proposed § 530.13 provides that allowable extralabel use by compounding applies only to compounding of a product from approved drugs by a veterinarian or a pharmacist on the order of a veterinarian within the practice of veterinary medicine, and that nothing in proposed part 530 is to be construed as permitting compounding from bulk drugs or unapproved drugs.

Additional guidance on the subject of compounding may be provided in guidance documents to be issued by FDA.

3. Sponsor Records, Reports, and Adverse Events

FDA is concerned that the enactment of the AMDUCA could have the unintended effect of reducing the information that has heretofore been provided to the agency by sponsors regarding their products.

Information that helps FDA assure the safe and effective use of approved drugs comes from two sources, among others. First, sponsors submit data and information on adverse events resulting from extralabel uses. Second, sponsors submit supplemental applications to extend the product labels to provide for new uses. The agency's concerns are

that under the AMDUCA the sponsors might have less incentive to submit supplemental applications, and might also be reluctant to report extralabel use adverse events that FDA could require to be stated in the labeling. FDA believes that neither result was intended by Congress. For example, the AMDUCA specifically requires the reporting of adverse events related to extralabel uses.

Section 512(l) of the act requires sponsors to maintain records of and report experiences ''and other data and information'' regarding a drug. Under 21 CFR 510.300 *et seq.*, ''Records and Reports,'' adopted under section 512(l) of the act, sponsors are currently required to report on extralabel drug uses. Section 2 of the AMDUCA amended section 512(l) of the act by adding new language specifically requiring maintenance of records and reports of experiences related to extralabel drug uses. Accordingly, the sponsor is required to maintain records of and report to the agency all information the sponsor has that pertains to extralabel drug uses, including adverse drug experiences.

Data derived from such records and reports may be used in establishing a prohibition against the use of a drug in food-producing animals under §§ 530.21 and 530.25, or safe levels and analytical methods under proposed §§ 530.22, 530.23, and 530.24. In addition, Section 2 of the AMDUCA amended section 512(e) of the act by adding new language specifically giving authority to the agency to withdraw approval of a NAD based on records and reports of experience with extralabel uses, in addition to experience with an approved use.

FDA believes that it is important to publicize data it has received concerning adverse events resulting from all uses, including extralabel drug uses. This could be done through provision of this information to professional journals, the trade press, and others, through press releases, ''Dear Doctor letters,'' and similar documents. FDA would be interested in receiving comments from the public with respect to any policy that would allow or encourage sponsors to provide extralabel drug use information regarding significant adverse events on labeling.

D. Advertising and Promotion Prohibited

While the AMDUCA and the proposed rule permit extralabel uses of approved drugs, neither the statute nor the proposed rule would permit advertising and promotion of extralabel uses. The act does not permit advertising and promotion of an unapproved use for a human or approved animal drug because scientific data supporting the safety and efficacy of a new drug use must be submitted by the sponsor and reviewed and approved by the agency in order to permit such use to be advertised, promoted, or included on the labeling. Advertising and promoting of any unapproved use for a drug would be inconsistent with the act and would subvert the entire system of drug approval and regulation because there would no longer be any incentive for a sponsor to submit data and go through the approval process for an unapproved use.

Accordingly, proposed § 530.4 includes a statement that the rule shall not be construed as permitting advertising or promotion of extralabel uses of human or new animal drugs.

E. Access to Veterinarian Records

Section 2(a) of the AMDUCA adds a new section 512(a)(4)(C) to the act which provides that FDA may adopt regulations providing FDA the right of access to records maintained by veterinarians to ascertain any extralabel use or intended use of an approved animal drug authorized by the agency that may present a risk to the public health.

Proposed § 530.5 provides that persons designated by FDA (i.e., FDA investigators) would be given access to the records of veterinarians, including records required to be maintained under the act, State veterinary practice acts, and State pharmacy acts. Any person who has custody of these records would be required to permit inspection at any reasonable times, permit copying, and verify such records.

While the AMDUCA does not include an explicit authority for FDA to require the creation and maintenance of records by veterinarians, the statute clearly allows the agency to specify the conditions for extralabel use. The agency believes that the maintenance of records is essential to the agency's ability to implement the statute and protect the public health and, as such, maintenance of records is a condition of allowable extralabel use. However, it is not FDA's intention to create new recordkeeping burdens on veterinarians who are required to keep records under State recordkeeping requirements.

FDA believes that these State required records will include the type of information FDA will need to carry out its statutory responsibilities. Records required by State veterinary practice acts or State pharmacy acts routinely document the existence of a valid veterinarian-client-patient relationship. These records also would provide relevant information concerning extralabel drug uses. Typically, these records include: (1) The name, address, and telephone number of the veterinarian; (2) the name, address, and telephone number of the client; (3) the complaint, or other reason for the provision of services, including information on the patient history, physical examination, and laboratory data; (4) the provisional or final diagnosis and date of diagnosis; (5) identification of the animal(s) treated (including species, breed, age, sex, color, brand, and tag or tattoo number); (6) the date of treatment, prescribing, or dispensing of the drug; (7) the established name of the drug and its active ingredient, or if formulated from more than one ingredient, the established name of each ingredient; the dosage form, strength, and quantity of the prescribed or dispensed drug, and the dates of administration; (8) any directions for use provided, including dose, route of administration, and length of therapy; (9) the number of refills authorized; (10) cautionary statements, if any; and (11) the veterinarian's specified withdrawal, withholding, or discard time(s), if applicable, for meat, milk, eggs, or any food that might be derived from any food animals treated.

Under the proposal, veterinarians would be required to maintain individual records for each nonfood animal treated as required by State veterinary practice and pharmacy acts. State veterinary practice acts generally require veterinarians in large animal practices to maintain records for food-producing animals that are adequate to substantiate the identification of the animals and the medical care provided. Such records in large animal practices can usually be maintained either as individual records or on a group, herd, flock, or per-client basis.

State veterinary practice and State pharmacy acts generally require veterinarians to maintain complete records of receipt and distribution of each veterinary drug. These records, which are maintained in the form required by the appropriate State acts, may include sales invoices, shipping records, prescription files, or records or logs established solely for this purpose. Receipt and distribution records usually are also required to include: (1) The name of the drug, (2) the name and address of the person or corporation from whom the drug was shipped, (3) the date and quantity received, and (4) the name and address of the person to whom the drug was distributed.

Under the proposed rule, drug distribution and use records would be required to be maintained for 2 years or as otherwise required by Federal or State law, whichever is greater.

The proposal would require that veterinarians maintain all records required by State veterinary practice and pharmacy acts in a legible form, document them in an accurate and timely manner, and keep them readily accessible to permit prompt retrieval of information.

Refusal to provide access to such required records is a prohibited act under section 301 of the act as amended by the AMDUCA.

F. Provision Permitting Extralabel Use of Animal Drugs

Proposed § 530.10 provides that extralabel use of an approved human or NAD is permitted by or under the lawful written or oral order of a veterinarian within the context of a veterinarian-client-patient relationship, if the extralabel use is otherwise in compliance with the regulation.

G. Limitations

Proposed § 530.11 sets out the following specific limitations on extralabel use. The following uses result in the drug being deemed to be unsafe within the meaning of the act: (1) Extralabel use in an animal of an approved new animal or human drug by a lay person (except under the supervision of a veterinarian), (2) extralabel use of an approved NAD or human drug in or on an animal feed, (3) extralabel use resulting in any residue which may present a risk to public health, and (4) extralabel use resulting in any residue above an established safe level or tolerance.

H. Labeling

The proposal at § 530.12 would require that any human or animal drug prescribed or dispensed for extralabel use by a veterinarian or a pharmacist on the order of a veterinarian bear or be accompanied by labeling information adequate to assure the safe and proper use of the product. The phrase ''be accompanied by'' is intended to permit shipment of drugs by a veterinarian or pharmacist on the order of a veterinarian in case quantities. The minimum information required under the proposal is the same as that currently required by CPG and includes: (a) The name and address of the 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 in which it 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 food that might be derived from the treated animal.

I. Specific Provision for New Animal Drug Extralabel Use in Food Animals

Proposed § 530.20(a)(2) requires as a condition for extralabel use that a veterinarian be required to take a number of affirmative actions before prescribing or dispensing an animal or human drug for an extralabel use in food animals. The veterinarian must do the following: (1) Make a careful diagnosis and evaluation of the conditions for which the drug is to be used; (2) establish a substantially extended withdrawal period prior to marketing of milk, meat, or eggs supported by appropriate scientific information, if applicable; (3) institute procedures to assure that the identity of the treated animal or animals is carefully maintained; and (4) 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.

Because extralabel use of drugs in food-producing animals engenders an increased potential for illegal drug residues in meat, milk, and eggs, which are consumed in significant amounts by the American public, the proposed rule would also set forth additional conditions for extralabel drug use in food-producing animals.

One restriction, contained in proposed § 530.20(b), applies to the extralabel use of either an approved human drug, or an animal drug approved only for use in animals not intended for human consumption. In such instances, records maintained by the veterinarian must reflect the medical rationale for such use. In addition, if there is no published scientific information on public health aspects of the use of the nonfood animal drug in food-producing animals, the veterinarian must determine that the animal and its food products will not enter the human food supply.

A second restriction would apply only to the use of human drugs in food animals. As discussed in section II.C. of this document, proposed § 530.20(a)(1) would not allow such use if an approved animal drug is available for such use (with certain exceptions). Section 530.20(c) requires the additional step of consideration of extralabel use of approved food-animal drug before use of a human drug or drug approved for use in animals not intended for human consumption. In addition, records maintained by the veterinarian must reflect this consideration.

J. Prohibitions, Safe Levels, Analytical Methods

Section 512(a)(4)(B) and (a)(4)(D) of the act as added by the AMDUCA grants FDA the authority to prohibit extralabel drug uses, establish safe levels and require the development of analytical methods. These provisions are included in section 512(a)(4) of the act which addresses approved NAD's and are not specified in section 512(a)(5) which addresses approved human drugs. Nevertheless, FDA believes that, under the general authority in section 512(a)(5) of the act to set the conditions for extralabel use of approved human drugs in animals, the agency may also set safe levels, require development of analytical methods, and prohibit extralabel uses of human drugs when necessary to protect the public health. Thus, the proposed rule applies these safeguards to human drugs as well as animal drugs.

Proposed § 530.21 addresses food-producing animals and states that FDA can prohibit the use of a drug or class of drugs in food-producing animals if the agency 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 use of the drug or class of drugs presents a risk to public health. Under the proposal, a prohibition may be a general ban on the use of the drug or class of drugs in all food-producing animals, or may be limited to a specific species, indication, dosage form, route of administration, or combination of factors.

Under proposed § 530.22, FDA could establish a safe level for extralabel use of a drug upon a finding that there is a reasonable probability that an extralabel use may present a risk to the public health. To accomplish this, the agency may: (1) Establish a finite safe level based on residue and metabolism information (i.e., toxicological data) 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 bases.

The proposal allows FDA to require the development of an acceptable analytical method for the quantification or detection of residues. If FDA requires such a method, the agency would

announce that requirement in the Federal Register. If development of an acceptable analytical method is required and a method is not developed, submitted, and accepted, the agency could, under the proposal, prohibit the extralabel use of the drug in food-producing animals.

The proposed rule provides, however, that if the agency establishes a safe level and a tolerance is later established through an approval for a particular species or category of animals, the safe level is superseded by the tolerance for that species or category of animals.

The proposed rule contemplates that FDA: (1) Will establish safe levels and publish them in the Federal Register, and (2) may establish specific analytical methods for drug residue detection for those drugs for which safe levels have been established. The safe levels and the availability of an analytical method will be codified at proposed § 530.40.

Proposed § 530.23 states that FDA will publish a document establishing a safe level in the Federal Register. This document would include 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 public health, and would request public comments.

Under the proposed rule, FDA would codify in proposed § 530.40 the following: (1) A current listing of those drugs for which a safe level for extralabel drug use in food-producing animals has been set, and (2) the specific safe levels, and the availability, when one has been developed, of a specific analytical method or methods for drug residue detection.

Proposed § 530.24 provides that copies of analytical methods would be made available upon request from the Center for Veterinary Medicine's Communications and Education Branch (HFV–12), 7500 Standish Pl., Rockville, MD 20855, and that acceptable analytical methods will be incorporated by reference.

While the agency does not intend to engage in prior notice and comment rulemaking for the establishment or acceptance of analytical methods or safe levels, interested persons will have the opportunity to make public comment to the agency as these actions are announced and published that could, if appropriate, result in modifications to the actions.

Proposed § 530.25 provides that FDA could issue an order prohibiting extralabel use of a drug in food-producing animals if the agency finds, after providing an opportunity for public comment, that: (1) An acceptable analytical method has not been developed, submitted, and found to be acceptable by FDA; or (2) an extralabel use in animals of a particular human drug or animal drug presents a risk to the public health.

After making a preliminary determination that a required analytical method has not been developed and submitted, or an extralabel use in food-producing animals of a particular human drug or animal drug presents a risk to the public health, FDA would, under the proposal, publish an order of prohibition with a 90-day delayed effective date in the Federal Register. Such order would specify the nature and extent of the order of prohibition and the reasons for the prohibition, and provide a period of not less than 60 days for comments.

The order of prohibition would become effective 90 days after the date of publication of the order of prohibition unless FDA publishes a Federal Register document before that date revoking the order of prohibition, modifying it, or extending the period of public comment.

The proposed rule would permit the agency to publish an order of prohibition with an abbreviated comment period and/or delayed effective date 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 sets forth the exceptional circumstances and the agency's rationale for taking such action.

Under the proposal, a current listing of drugs prohibited for extralabel use in food-producing animals would be codified in new § 530.41.

The proposed rule would also note that the agency could, after publishing a Federal Register document, remove a drug from the prohibited list after the submission of appropriate information, such as adequate safety and effectiveness data, an acceptable method, approval of a new animal drug application for the prohibited drug and use, or information demonstrating that the prohibition was based on incorrect data.

K. Extralabel Drug Use in Nonfood Animals

Because the same public health implications do not exist in the treatment of nonfood animals as for food animals, the proposed rule does not include the same level of detail for such extralabel use. Specifically, proposed § 530.30 provides that veterinarians can make extralabel use or dispensing of drug products in nonfood-producing animal practice except when such use may threaten the public health. One other limitation, as discussed earlier in the preamble, is that, if an approved NAD for such use exists, an extralabel use of an approved animal or human drug is not permitted. (See proposed § 530.30(a).)

The proposal adds that the agency may publish a document in the Federal Register prohibiting a particular extralabel drug use in nonfood animals if the agency determines that it presents a risk to the public health. This provision is consistent with the agency's authority to establish conditions for extralabel use of human drugs under the AMDUCA.

III. Proposed Effective Dates

Under Section 2(d) of the AMDUCA, the amendments to the act permitting the extralabel use of certain approved animal drugs and approved human drugs for animals become effective upon the adoption of final rules implementing the amendments. FDA intends that any final rule that may issue based on this proposal become effective 30 days after the date of publication in the Federal Register.

IV. Environmental Impact

The agency has determined under 21 CFR 25.24(a)(8) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

V. Analysis of Impacts

FDA has examined the impacts of the proposed rule under Executive Order 12866 and the Regulatory Flexibility Act (Pub. L. 96–354). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). The agency believes that this proposed rule is consistent with the regulatory philosophy and principles identified in the Executive Order. In addition, the proposed rule is not a significant regulatory action as defined by the Executive Order.

Most of the requirements in this proposed rule have already been implemented by regulated industry,

veterinarians, and pharmacists in response to the existing Compliance Policy Guides relating to extralabel drug use in animals and the passage of the AMDUCA, FDA guidance, and industry trade associations' recommendations, as well as the requirements of State veterinary practice acts and as customary elements of good veterinary medical practice.

The actual cost to industry and the public associated with this proposal will be quite minimal. The AMDUCA was enacted to decriminalize extralabel use of most approved new human and animal drugs in veterinary medicine, and to provide FDA with specific regulatory tools to assure food safety. Congress intended that the new legislation codify FDA's discretionary enforcement policies that have permitted extralabel use of approved new human and animal drugs by veterinarians in specified circumstances.

FDA is likely to require the establishment of a safe level for one to two drugs per year after the proposed rule is finalized. An analytical methodology for drug residue detection will be required for each of these drugs. The sponsor may be willing to provide the methodology in some cases, while in others, FDA, the sponsor, and, perhaps, a third party, may negotiate a cooperative arrangement for methodology development. The range of costs for development of methodologies is likely to range from about $90,000 for a drug for which there are few problems in developing a procedure, upward to about $350,000 for a drug which presents significant problems in methodology development, with an additional $100,000 required for a drug metabolism study. Methodology development costs for a drug presenting an intermediate level of difficulty would be about $170,000. The agency estimates that the average year would see the development of two drug methodologies presenting an intermediate level of development difficulty, with one of those drugs requiring a metabolism study, for an annual cost impact of about $440,000. The proposal does not impose any new extralabel drug use recordkeeping and reporting requirements for sponsors or veterinarians which are not currently required under other sections of the act or under State veterinary practice acts.

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a proposed rule on small entities. Because the proposed rule clarifies existing FDA policy, and because most of the requirements in this proposed rule have already been implemented by regulated industry, veterinarians, and pharmacists in response to the existing Compliance Policy Guides relating to extralabel drug use in animals and the passage of the AMDUCA, FDA guidance, and industry trade associations' recommendations, the agency certifies, in accordance with section 605(b) of the Regulatory Flexibility Act, that the proposed rule will not have a significant economic impact on a substantial number of small entities. Therefore, under the Regulatory Flexibility Act, no further analysis is required.

VI. Paperwork Reduction Act of 1995

This proposed rule contains reporting requirements that are subject to public comment and to review by OMB under the Paperwork Reduction Act of 1995 (Pub. L. 104–13). Therefore, in accordance with 5 CFR 1320, a description of reporting requirements is given below with an estimate of the annual collection of information burden. Included in the estimate is the time for reviewing instructions, gathering and maintaining the data needed, and completing and reviewing the collection of information.

With respect to the following collection of information, FDA is soliciting comments on: (1) Whether the proposed collection of information is necessary for proper performance of FDA's functions, including whether the information will have practical utility; (2) the accuracy of FDA's estimate of the burden of the proposed collection of information, including the validity of the methodology and assumptions used; (3) ways to enhance the quality, utility, and clarity of the information to be collected; and (4) ways to minimize the burden of the collection of information on respondents, including through the use of automated collection techniques, when appropriate, and other forms of information technology.

Title: Extralabel Drug Use in Animals.

Description: This proposed rule provides that FDA may require the development of an acceptable analytical method for the quantification of residues above an established safe level. FDA estimates that it will likely establish safe levels for one to two drugs per year if the rule is finalized, and that an analytical methodology for drug residue detection will be required for each of these drugs. If no method is provided, the Secretary may prohibit the extralabel use. This requirement may be fulfilled by any interested person. FDA believes that the sponsor may be willing to provide the methodology in some cases, while in others, FDA, the sponsor, and perhaps a third party may negotiate a cooperative arrangement for method development.

Description of Respondents: Persons, sponsors, States, or Federal Government.

ESTIMATED ANNUAL REPORTING BURDEN

21 CFR Section	No. Of Respondents	Annual Frequency per Response	Total Annual Responses	Hours per Response	Total Hours
21 CFR 530.22(b)	2	1	2	4,160	8,320

There are no operating and maintenance or capital costs associated with this information collection. The agency recognizes that the time and expense of method development is highly variable dependent on the difficulty of the development. The agency estimates that two methods of intermediate difficulty would be developed and these methods may take up to 2 person-years to develop.

The agency has submitted a copy of this proposed rule to OMB for its review and approval of this information collection. Interested persons are requested to send comments regarding this information collection, including suggestions for reducing this burden to the Office of Information and Regulatory Affairs, OMB, New Executive Office Building, 725 17th St. NW., rm. 10235, Washington, DC 20503, Attn: Desk Officer for FDA. Written comments on the information collection should be submitted by June 17, 1996.

VII. Federalism

FDA has analyzed this proposal in accordance with the principles and criteria set forth in Executive Order 12612 and has determined that this

proposal does not have sufficient federalism implications to warrant the preparation of a federalism assessment.

VIII. Request for Comments

Interested persons may, on or before July 31, 1996, submit to the Dockets Management Branch (HFA–305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1–23, Rockville, MD 20857, written comments regarding this proposal. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

List of Subjects in 21 CFR Part 530

Administrative practice and procedures, Advertising, Animal drugs, Animal feeds, Human drugs, Labeling, Prescription drugs, Promotion, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act, and under authority delegated to the Commissioner of Food and Drugs, it is proposed that Title 21 of the Code of Federal Regulations be amended to add a new part 530 to read as follows:

PART 530—EXTRALABEL DRUG USE IN ANIMALS

Subpart A—General Provisions

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

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

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

Subpart C—Specific Provisions Relating to Extralabel Uses 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.
Sec. 530.21 Prohibitions for food-producing animals.
Sec. 530.22 Safe levels and analytical methods for food-producing animals.
Sec. 530.23 Procedure for setting and announcing safe levels.
Sec. 530.24 Procedure for announcing analytical methods for drug residue quantification.
Sec. 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

Sec. 530.30 Extralabel drug use in nonfood animals.

Subpart E—Safe Levels for Extralabel Use in Animals and Drugs Prohibited for Extralabel Use in Animals

Sec. 530.40 Safe levels and availability of analytical methods.
Sec. 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

§ 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 veterinarian within the context of a valid veterinarian-client-patient relationship.

§ 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 veterinarians of 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).

§ 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.

(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 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.

§ 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.

§ 530.5 Veterinary records.

(a) Persons designated by FDA shall have access to the records of veterinarians, including records

required to be maintained under the act, State veterinary practice acts, and State pharmacy acts, to ascertain any extralabel use or intended extralabel use of drugs that the agency has determined may present a risk to the public health.

(b) As a condition of extralabel use permitted under this part, veterinarians shall maintain records as required by State veterinary practice and pharmacy acts. 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 the medical care provided and shall be maintained either as individual records or, in large animal practices, on a group, herd, flock, or per-client basis. As required by the State, such records will typically include, but not be limited to, the following information:

(1) The name, address, and telephone number of the veterinarian;

(2) The name, address, and telephone number of the client;

(3) The complaint, or other reason for the provision of services, including information on the patient history, physical examination, and laboratory data;

(4) The provisional or final diagnosis and date of diagnosis;

(5) Adequate identification of the animal(s) treated;

(6) The date or dates of treatment, prescribing, or dispensing of the drug;

(7) The established name of the drug and its active ingredient, or if formulated from more than one ingredient, the established name of each ingredient; the dosage form, strength, and quantity of the prescribed or dispensed drug, and the dates of administration;

(8) Any directions for use provided, including dose, route of administration, and length of therapy;

(9) The number of refills authorized;

(10) Cautionary statements, if any; and

(11) The veterinarian's 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.

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

(d) 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

§ 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 veterinarian within the context of a valid veterinarian-client-patient relationship; and

(b) In compliance with this part.

§ 530.11 Limitations.

In addition to uses which do not comply with the provision set forth in § 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 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 public health; and

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

§ 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 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 in which it 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 food which might be derived from the treated animal.

§ 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 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;

(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 provided in guidance documents issued by FDA.

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

§ 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.

(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, or eggs 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 an approved human drug, or of an animal drug approved only for use in animals not intended for human consumption, in food-producing animals:

(1) Records maintained by the veterinarian must reflect the medical rationale; and

(2) If there is no published scientific information on the public health aspect of the use of the drug in food-producing animals, the veterinarian must determine that the animal and its food products will not enter the human food supply.

(c) Extralabel use of an approved human drug in food-producing animals will not be permitted unless the veterinarian first considers the extralabel use of an approved animal drug for use in food-producing animals under the provisions of this part. Such consideration must be documented in the veterinarians' records.

§ 530.21 Prohibitions for food-producing animals.

(a) FDA may prohibit the 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 use of the drug or class of drugs presents a risk to public health.

(b) A prohibition may be a general ban on the 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.

§ 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 bases.

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

§ 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 public health, and

(2) 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 set, the specific safe levels, and the availability, if any, of a specific analytical method or methods for drug residue detection will be codified in § 530.40.

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

Copies of analytical methods for the quantification of extralabel use drug residues above the safe levels established under § 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 § 530.22 is developed, and that method is acceptable to the agency, FDA will incorporate that method by reference.

§ 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 § 530.22 of this part has not been developed, submitted, and found to be acceptable by FDA; 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 § 530.22 has not been developed and submitted, 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 will:

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

(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) 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 § 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 drug and 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

§ 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 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 § 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 § 530.25. The prohibited drug use will be codified in § 530.41.

Subpart E—Safe Levels for Extralabel Use in Animals and Drugs Prohibited for Extralabel Use in Animals

§ 530.40 Safe levels and availability of analytical methods.

In accordance with § 530.22, when the agency finds that there is a reasonable probability than an extralabel use may present a risk to the public health, FDA may establish by order a safe level for an extralabel use in animals of an approved human drug or an approved animal drug, and may establish a specific analytical method or methods for drug residue detection. FDA will publish in the Federal Register a notice of the order and the availability, if any, of an analytical method or methods for drug residue detection and will codify them in this section. This section will include the following: A current listing of those drugs for which a safe level for extralabel drug use in food-producing animals has been set, and the specific safe levels, and the availability, when one has been developed, of a specific analytical method or methods for drug residue detection.

§ 530.41 Drugs prohibited for extralabel use in animals.

In accordance with § 530.25, the following drugs are prohibited for extralabel use in animals:

Dated: May 8, 1996.

William B. Schultz,

Deputy Commissioner for Policy.

Note: The following appendix will not appear in the Code of Federal Regulations.

Appendix

Compliance Policy Guides

Chapter 6—Veterinary Medicine

Sec. 608.100 Human-Labeled Drugs Distributed and Used in Animal Medicine (CPG 7125.35)

Background

This Compliance Policy Guide explains how FDA will exercise its enforcement discretion with respect to distribution and use of human-labeled drug products for use in animals. It is FDA's intent to:

—eliminate promotion by manufacturers, distributors, and pharmacies;

—ensure that distribution and dispensing are made only in response to requests by veterinary practitioners (practitioner driven);

—refrain in ordinary circumstances from enforcement actions when human drugs are used or dispensed by veterinarians in treating non-food-producing animals;

—take enforcement action against veterinarians who cause illegal residues in food-producing animals;

—limit use of human-labeled drugs in treating food-producing animals to very narrow circumstances; and

—prohibit use except by or on the order of a licensed veterinarian in the course of his or her practice.

The key regulatory elements under this policy are determination of whether or not (1) the distribution and dispensing are practitioner driven and (2) the veterinary practitioners limit their uses of human-labeled drug products to treating non-food animals, with certain narrow exceptions. Because distribution and dispensing are to be veterinary practitioner driven, and because distributors and pharmacists, after properly distributing the drug, ordinarily cannot control end uses, this policy places primary responsibility on the veterinarian. This policy is not intended to permit the distribution of human-labeled drug products to veterinarians where prohibited or limited by State laws.

FDA is aware that human-labeled drug products have been promoted and distributed by manufacturers, distributors, and pharmacies for use in animals and that such drugs are being prescribed, dispensed, and administered by veterinarians for animal use.

Promotion of human-labeled drug products for veterinary use by these sources has included acts such as advertising animal use in veterinary publications; distribution of labeling and promotional materials suggesting or recommending use of these products in animals; or oral statements from sales personnel describing or recommending use in animals. Such promotion causes the drugs to be misbranded under Section 502(f)(1), or adulterated new animal drugs under Section 501(a)(5), or both. Furthermore, such promotion may subvert the New animal drug approval process by creating a disincentive for drug manufacturers to seek such approvals.

Most veterinary use of human-labeled drug products occurs in non-food animal practice (companion, sporting, exotic, etc.). Many of the maladies of pets and other non-food animals cannot be treated in accordance with current standards of veterinary practice without the use of human-labeled drugs since appropriate drug products bearing veterinary labeling often do not exist. Because of this, FDA has generally refrained from taking enforcement actions in this area because there is no expected adverse impact upon the public health.

FDA is very concerned about the use of human-labeled drugs in food-producing animals because of the increased potential for illegal drug residues in meat, milk, and eggs. Human-labeled drug products have not, among other things, undergone testing for residue depletion from edible tissues. Appropriate withdrawal times to avoid illegal residues in food can only be estimated.

Nevertheless, there are legitimate and important veterinary needs for human-labeled drugs in the treatment of disease or to prevent pain in food-producing animals in instances where there simply are no animal drug products available that would avoid animal suffering or death. Examples include, but are not necessarily limited to analgesics and anesthetics for pain, sedation, and surgery, insulin for ketosis, and antidotes for poisonings.

Policy

A. Distribution and Dispensing

Labeling, advertising, oral representations, or any other act by a manufacturer, distributor, or pharmacy which establishes an intended use of human-labeled drugs for animal use is subject to regulatory action. However, the simple listing of human-labeled drug products in price sheets and catalogues distributed to veterinarians will not ordinarily be subject to such action. Dispensing pharmacists are required by Section 503(f) to label dispensed drugs in accordance with the prescribing veterinarian's instructions, including the name and address of the dispenser, the serial number and date of the order or of its filing, the name of the licensed veterinarian, and directions for use and any cautionary statements. Providing this information does not constitute promotion against which the agency is prepared to take action.

High priority will be placed on actions against manufacturers, distributors, and pharmacies who promote the substitution of human-labeled drug products for animal drugs for economic reasons.

B. Use of human drugs by veterinarians in professional practice

(i) Use in non-food-producing animals; e.g., dogs, cats, horses.

Under usual circumstances, veterinary practitioners may consider

the use of human-labeled drug products in non-food-producing animal practice without the threat of FDA enforcement actions. In rare circumstances, for example, when the health of the treated animals is harmed, regulatory attention by FDA would be considered or, preferably, referred to the State veterinary licensing authority for investigation.

(ii) Use in food-producing animals; e.g., cattle, swine, poultry.

Use of human-labeled drug products in food-producing animals should be extremely limited, primarily because of the increased potential for illegal drug residues in meat, milk, and eggs. For example, it is ordinarily unacceptable to use a human-labeled product for common disease conditions in food animals because approved veterinary-labeled drug products; e.g., antibacterials, anti-inflammatory agents, etc. are available. The food animal veterinarian assumes greater responsibility when he or she uses a human drug rather than a veterinary drug. Use of human-labeled drugs may be considered by food animal veterinarians only when they have:

—made a careful and definitive diagnosis and evaluation of the condition for which the drug is to be used, and are otherwise operating within the confines of a veterinarian/client/patient relationship;

—made a deliberate determination that there is no other appropriate veterinary-labeled therapy; i.e., there is no marketed veterinary labeled drug product specifically labeled for the disease condition to be treated or the veterinary drug has been found clinically ineffective by the veterinarian in the animals to be treated; and

—taken adequate steps to prevent the occurrence of illegal residues in edible animal products. This should include a review of the best available toxicological and tissue distribution and tissue residue depletion data and establishment of an extra long drug withdrawal period prior to marketing meat, milk, or eggs. The animal owner or manager should be given explicit written withdrawal instructions. The practitioner should have a high degree of confidence that the client will follow the drug withdrawal instruction.

Regulatory action should be considered when an illegal residue occurs even if the veterinarian followed the foregoing precautions. The enforcement discretion that might be accorded to veterinarians will not be extended to lay persons; e.g., owners, who administer human-labeled drugs either to food-producing or nonfood animals without the supervision of a licensed veterinarian operating within the framework of a valid veterinarian/client/patient relationship.

Veterinarians are expected to follow cautionary handling and disposal provisions, if any, specified in human drug labeling to protect handlers and the environment.

Regulatory Action Guidance

The highest priority for regulatory attention is for follow-up on reports of illegal tissue residues from human-labeled drugs. Follow the instructions in Compliance Program 7371.006, *Illegal Drug Residues in Meat and Poultry* and Compliance Program 7371.008, *National Drug Residue Milk Monitoring Program*. Consultation with Case Guidance Branch for guidance under this policy is indicated when encountering other suspected violations, especially where there is substitution of human-labeled drugs for treatment of common disease conditions in food animals.

The initial enforcement action of choice is ordinarily a Warning Letter. Center concurrence is required prior to issuance. Depending on the circumstances, one or more of the following charges would be appropriate.

—402(a)(2)(D)-food adulterated by illegal residue from a new animal drug;

—402(a)(2)(A)-food adulterated by illegal residue from a human-labeled drug;

—501(a)(5)-adulterated drug (labeled for human use which is accompanied by labeling indicating it for animal use which causes it to be unsafe under Section 512(a) as an unapproved new animal drug);

—502(f)(1)-misbranded human drug when not used as labeled; misbranded human drug promoted for animal use in ways other than by labeling (see 21 CFR 201.128).

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Sec. 615.100 Extralabel Use of New Animal Drugs in Food-Producing Animals (CPG 7125.06)

Background

Concern over the extralabel use of drugs in treating food-producing animals and the possibility that human food may become adulterated with illegal drug residues from such misuse has prompted a revision in the Center for Veterinary Medicine (CVM) extralabel drug use policy. Under the revised policy, a finding of illegal drug residues no longer will be a prerequisite for initiating regulatory action based on extralabel drug use of drugs in food-producing animals.

For the purpose of this policy, ''extralabel use'' refers to the actual or intended use of a new animal drug in a food-producing animal in a manner that is not in accordance with the drug labeling. This includes, but is not limited to, use in species or for indications (disease or other conditions) not listed in the labeling, use at dosage levels higher than those stated in the labeling, and failure to observe the stated withdrawal time.

FDA in the past has not sanctioned extralabel uses of drugs in food-producing animals, but the agency has stated that it would refrain from instituting regulatory action against licensed veterinarians for using or prescribing in their practices any drugs they could legally obtain. Nevertheless, it has been FDA's position that veterinarians may be subject to regulatory action for any violative drug residues in human food resulting from their prescriptions, recommendations, or treatments contrary to label instructions. Similarly, anyone in the producing or marketing chain who could be shown to have caused illegal drug residues through extralabel use of drugs in food-producing animals has been subject to regulatory action.

In contrast, under usual circumstances veterinary practitioners may consider the extralabel use of drug products in non-food-producing animal practice without being subject to FDA enforcement actions. In rare circumstances, for example when the health of the treated animals is harmed, regulatory attention by FDA would be considered or, preferably, referred to the State veterinary licensing authority for investigation.

Policy

The use or intended use of new animal drugs in treating food-producing animals in any manner other than in accord with the approved labeling causes the drugs to be adulterated under the Federal Food, Drug, and Cosmetic Act (the Act) (sections 501(a)(5) and (6), 512(a)(1)(A) and (B), 512(a)(2)). The agency will consider regulatory action when such use or intended use is found, whether by a veterinarian, producer, or other person. Regulatory actions will also be considered against distributors and others who might cause adulteration of approved new animal drugs. Nevertheless, extralabel drug use in treating food-producing animals may be considered by a veterinarian when the health of animals is immediately threatened and suffering or death would result from failure to treat the affected animals. In instances of this nature, regulatory action would not ordinarily be considered provided all [at] the following criteria are met and precautions observed:

1. A careful medical diagnosis is made by an attending veterinarian within the context of a valid veterinarian-client-patient relationship;* * *

2. A determination is made that (a) there is no marketed drug specifically labeled to treat the condition diagnosed, or drug therapy at the dosage recommended by the labeling has been found clinically ineffective by the veterinarian in the animals to be treated;

3. Procedures are instituted to assure that identity of the treated animals is carefully maintained;

4. Significantly extended time period is assigned for drug withdrawal prior to marketing meat, milk, or eggs; steps are taken to assure that the assigned time frames are met, and no illegal residues occur; and

5. The prescribed or dispensed extralabel drug (prescription legend or over the counter) bears labeling information which is adequate to assure the safe and proper use of the product. At a minimum, the following label information is recommended:

a. The name and address of the veterinary practitioner.

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

c. Any 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).

d. Any cautionary statements specified by the veterinarian.

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

Extra-label use of drugs in treating food-producing animals may under this policy, therefore, be considered only in special circumstances. The ''exempting'' criteria do not include drug use in treating food-producing animals by the layman. Lay persons cannot be expected to have sufficient knowledge and understanding concerning animal diseases, pharmacology, toxicology, drug interactions, and other scientific parameters to use drugs in treating food-producing animals in any way other than as labeled.

Certain drugs may not be used in treating food-producing animals even under the cited criteria. This includes chloramphenicol. Extralabel uses of drugs in treating food-producing animals for improving rate of weight gain, feed efficiency, or other producing purposes, or for routine disease prevention are inappropriate as is use for therapeutic purposes other than under the circumstances described above. Also, the criteria cited above do not sanction the sale and use, for any purpose, of new animal drugs that are not approved, such as diethylstilbestrol (DES). Furthermore, a drug (including a bulk drug) may not be mixed into feed for any use or at a potency level not specifically permitted by the regulations in 21 CFR Part 558, even if prescribed or ordered by a veterinarian.

Regulatory Guidance

The highest priorities for regulatory attention regarding extra-label use are:

1. Instances where illegal residues occur.

2. In all food-producing animals:

Chloramphenicol

Clenbuterol

Diethylstilbestrol (DES)

Dimetridazole

Ipronidazole

Other nitroimidazoles

Furazolidone (Except for approved topical use)

Nitrofurazone (Except for approved topical use)

3. In lactating dairy cattle:

Sulfonamide drugs (except approved use of sulfa-dimethoxine, sulfabromomethazine and sulfaethoxy-pyridazine)

4. Manufacturers and distributors who promote extra-label use of drugs.

5. The mixing of drugs into medicated feeds intended for extra-label use.

6. Extra-label use by laymen at their own initiative.

* * *A valid veterinarian-client-patient relationship, as defined by the American Veterinary Medical Association is the following: An appropriate veterinarian-client-patient relationship will exist when: (1) the veterinarian has assumed the responsibility for making medical judgements regarding the health of the animal(s) and the need for medical treatment, and the client (owner or other caretaker) has agreed to follow the instructions of the veterinarian; and when (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). This means that 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 when (3) the practicing veterinarian is readily available for follow-up in case of adverse reactions or failure of the regimen of therapy.

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