

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.

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SUPPLEMENTARY INFORMATION:**I. Background**

On October 22, 1994, the President signed into law the AMDUCA (Pub. L. 103-396). Prior to enactment of the AMDUCA, section 512 of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 360b) had provided that a new animal drug (NAD) was deemed unsafe unless it was 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 forth 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 of the act 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 the 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 the 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 the 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 there is an approved 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. The AMDUCA amends section 301(e) of the act to provide that failure to maintain records or provide access to records of veterinarians, as provided by general regulations, 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 final rule, any amount of residue that may present a risk to the 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

provisions of the AMDUCA are effective upon adoption of a final rule implementing the statute. The AMDUCA requires publication of a final rule within 2 years of the date of enactment.

As noted in the preamble to the proposed rule, until publication of a final implementing rule makes the AMDUCA effective, extralabel use of drugs in animals continues to be a violation of the act. FDA's existing enforcement policies relating to extralabel use have been described in two FDA Compliance Policy Guides (CPG's) entitled "Extralabel Use of New Animal Drugs in Food-Producing Animals" and "Human-Labeled Drugs Distributed and Used in Animal Medicine." The extralabel CPG's were issued to provide information and direction to FDA personnel in the field about the circumstances in which FDA would ordinarily take regulatory action against extralabel use of approved NAD's and human drugs in animals and those situations in which the agency would ordinarily exercise its regulatory discretion and not take action.

The scant legislative history of the AMDUCA includes evidence that the AMDUCA was intended to codify policies similar to those in FDA's CPG's. The agency has generally followed policies similar to those in the existing CPG's in this final rule. It is anticipated that these CPG's will be withdrawn after this final rule is published. FDA may, as necessary, issue additional CPG's or other guidance related to extralabel use of animal and human drugs.

II. The Proposed Rule**A. Summary of the Proposed Rule**

In the Federal Register of May 17, 1996 (61 FR 25106), FDA published a notice of proposed rulemaking to implement the AMDUCA. The rule as proposed 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.

Consistent with the policies expressed in the CPG's, the proposed rule limited 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. The proposal asked for comment on requests

to permit extralabel drug use for some nontherapeutic uses, but did not provide for such uses.

The proposed rule included a number of definitions, including definitions for the phrases "a reasonable probability that a drug's use may present a risk to the public health," "use of a drug may present a risk to the public health," and "use of a drug presents a risk to the public health." In defining these phrases, the agency considered the common meaning of the words in these phrases, and other regulations in which FDA has defined similar concepts.

The proposed rule reiterated the statutory prohibition against the advertising and promotion of extralabel drug uses. It provided for the inspection of veterinary records by FDA investigators, including records required under the act and regulations and State veterinary practice and pharmacy acts, to ascertain any extralabel use that the agency has determined may present a risk to the public health. The proposed rule specified particular extralabel uses that are not permitted, i.e., extralabel use by a lay person (except when under a veterinarian's supervision), extralabel use in or on an animal feed, extralabel use resulting in any residue which may present a risk to the public health, and extralabel use resulting in any residue above an established safe level or tolerance. The proposal also included labeling requirements. In addition, it provided conditions for compounding of approved NAD's and approved human drugs.

The proposal would require the prescribing or dispensing veterinarian to: (1) Diagnose and evaluate the conditions; (2) establish a substantially extended withdrawal period prior to marketing of milk, meat, or eggs supported by appropriate scientific information; (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. The proposal included some additional conditions for permitted extralabel uses in food animals of a human drug, or of an NAD approved only in use in nonfood animals.

The proposal also stated that FDA may prohibit the extralabel use of an approved new animal or human drug in food-producing animals if FDA determines that an acceptable analytical method needs to be established and this method has not been established or cannot be established, or use of the drug presents a risk to the public health. It added that 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.

The proposed rule also included procedures for establishing and announcing safe levels, for developing analytical methods, and for issuing orders prohibiting extralabel uses of drugs in food-producing animals. The proposed rule also included provisions regarding extralabel drug use in nonfood animals.

In addition to publishing the proposed rule in the Federal Register, FDA gave notice of the publication of the proposed rule by various additional means and invited comments. The comment period for the proposed rule lasted 75 days, closing July 31, 1996. Several requests for an extension of the comment period were denied to enable the agency to meet the statutory deadline for publishing the final rule.

B. Discussion of Comments

FDA received approximately 110 comments on the proposed rule. A discussion of the comments and FDA's responses follows:

1. Issues on Which FDA Requested Comment

(1) The agency invited comment as to whether extralabel use should be permitted when an approved drug is found by the veterinarian to be ineffective in a particular clinical situation. 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 animal drug CPG contains an exception that permits an extralabel use where the veterinarian finds, within the context of a valid veterinary-client-patient relationship, that an approved NAD is clinically ineffective for its intended use. However, neither the statute nor the proposed rule contained a similar provision.

A large number of comments contended that the regulations should provide such an exception. The comments stated that veterinarians frequently encounter clinical situations in which an approved drug is ineffective. One comment observed that approved drugs are effective under labeled conditions in most circumstances, so that it would not be inconsistent with the approval provisions of the act to provide for extralabel use in specific situations in which a drug is ineffective under labeled conditions. The comment

asserted that the AMDUCA is intended to codify policies similar to those in the CPG's, such as the "clinically ineffective" provision.

FDA recognizes that the AMDUCA does not provide any explicit exceptions to its prohibition against extralabel drug use when an approved NAD with the same active ingredient in the same dosage form and concentration exists for that use. The agency believes, however, that not allowing extralabel drug use in situations in which the approved NAD is clinically ineffective would produce an absurd result. Under established principles of statutory construction, a statute should be construed to avoid an absurd result. (See e.g., *Rowland v. California Men's Colony*, 113 S. Ct. 716, 720 (1993).)

Under the act, an NAD can be found to be effective even though the drug may not be effective in treating all target animals for the labeled indication. The statute requires that there be substantial evidence that an NAD is effective for its labeled indications. The legislative history of the 1962 Amendments, which added the effectiveness standard to the act, indicated that evidence sufficient to meet the "substantial evidence" standard could be met where "the studies * * * show that the drug will help a substantial percentage of patients in a given disease condition but will not be effective in other cases." (See S. Rept. 1744, 87th Cong. 2d sess., Part 1 at 16 (1962).) For those cases in which an approved NAD is not clinically effective, it is as if the drug does not exist for that condition. Under the AMDUCA, if there is no approved NAD for a particular condition, veterinarians are allowed to use a drug extralabelly; however, veterinarians would not be allowed to use a drug extralabelly in essentially the same situation, that is, when the approved NAD is clinically ineffective.

Therefore, the agency has concluded that, under the AMDUCA, allowing extralabel drug use when the approved NAD is clinically ineffective is legally supportable. The agency cautions, however, that veterinarians must have a basis for determining that the use of the approved NAD is clinically ineffective in the animal or animals involved. Unsupported claims of clinical ineffectiveness will not be allowed to circumvent the statutory prohibition against extralabel drug use when an approved NAD for that condition exists. Proposed § 530.20(a)(1) has been amended to provide for extralabel drug use in the case of an approved NAD that is clinically ineffective.

(2) The agency asked for comment as whether extralabel use of animal and

human drugs should be permitted for nontherapeutic uses such as improved reproductive responses in terrestrial and, especially, in aquatic food-producing animals.

More than a dozen organizations and several individuals advocated extralabel use for all reproductive purposes. One comment objected to the concept, several comments could be interpreted to be in opposition, and one other comment urged the agency to be extremely judicious in granting such an exception. Reasons advanced for allowing reproductive-related extralabel uses included: All reproductive uses are therapeutic; drugs used for reproductive purposes pose little human food safety threat, and in fact some broodstock (e.g., broodfish) can be considered nonfood animals; reproductive use of drugs is especially important in minor species (e.g., aquaculture) and other limited situations (e.g., contraceptive uses in nuisance animals and free ranging wildlife) for which few drugs are approved; and extralabel use of reproductive drugs conserves animal resources, and allows application of new technology (e.g., embryo transfer and artificial insemination).

The agency agrees that the comments have identified some important reasons for extralabel use of drugs for nontherapeutic reproductive purposes. The agency believes that some, but not all, reproductive-related drug uses are therapeutic and would be permitted under the final rule. However, after further consideration the agency has concluded that the statute is not intended to provide for extralabel use of drugs for nontherapeutic purposes. For example, Senator Coats identified the problem of the AMDUCA was intended to address as "too few approved animal health products to treat all animal illnesses," as such:

in order to treat animals adequately and to alleviate animal suffering, veterinarians must use some products in an extra-label fashion * * * [AMDUCA] is at best a short-term solution to a long-term and larger problem—the lack of drugs available to treat animals. The legislation, as it passed, will not address this problem * * * [W]e must address the larger and increasingly urgent problem of animal drug availability.

(140 Congressional Record S14272 (daily ed. October 5, 1994).)

The agency believes that including nontherapeutic uses in these final rules is beyond the scope of the AMDUCA's intent to allow the legal use of drugs extralabelly to treat animal illnesses. Allowing nontherapeutic uses would extend the AMDUCA's scope into the animal drug availability issues, issues that Congress reserved to address at another time. In this regard legislation was recently enacted, the Animal Drug Availability Act of 1996 (Pub. L. 104-250), that is intended to streamline the animal drug approval process to increase the availability of approved animal drugs. The new legislation should decrease the need for extralabel use of drugs as more animal drug products for both therapeutic and nontherapeutic uses are approved. The agency also notes that it anticipates examining extralabel use which is not covered by the AMDUCA, such as nontherapeutic extralabel drug use, in the context of determining regulatory priorities. The agency will either issue another CPG or determine on a case-by-case basis those situations, if any, which fall outside the scope of the AMDUCA that would be of low regulatory priority.

(3) One comment, from the American Association of Swine Practitioners (AASP), advocated extralabel use for what the association called "therapeutic preventative medicine." An example would be extralabel use for medicated early weaning and segregated early weaning of pigs, to avoid morbidity or death loss that can be quite high among weaned pigs if treatment is delayed until clinical signs appear. AASP noted that the preventive extralabel use is appropriate in those clinical situations in which the veterinarian is well acquainted with the production system, the profile of the animals and the diseases present or likely to occur. The agency agrees that as long as the health of the animals is threatened, extralabel uses for preventive purposes is acceptable. The proposed rule did not include the word "immediately," which had appeared before the word "threatened" in the CPG. This change was made to make it clear that preventive uses when the health of the animal is threatened are permitted. However, the agency cautions that the veterinarian must have a rational basis, such as that cited by AASP in the case of weaned pigs, for determining that the health of the animals is actually threatened. Also, preventive extralabel use would be subject to other restrictions in the regulations, such as restrictions on extralabel use of drugs administered in feed.

(4) The agency asked for comment on appropriate ways to balance extralabel use with the need to preserve the goal of increased availability of NAD's approved for such uses under section 512 of the act. Although the agency made the request in connection with its discussion of nontherapeutic extralabel uses, the comments addressed the issue more generally.

The American Veterinary Medical Association (AVMA) stated that Congress, by permitting use of a less expensive approved human drug in companion animals when an approved NAD is available, placed higher priority on reducing costs to consumers and pet owners than on incentives for drug manufacturers. The comment stated that this emphasis is appropriate because "the real problem of animal drug availability pertains to approved animal drugs for use in food animals." With regard to food animals, AVMA and AASP emphasized the need for extralabel uses for which the market is extremely small and therefore would provide little financial incentive to drug manufacturers even if extralabel use were restricted. The Animal Health Institute (AHI), which represents a number of animal drug manufacturers, focused on what it called a double standard created by the proposed regulations. According to AHI, the regulations allow the veterinarian to determine whether a drug is safe, until FDA determines otherwise; on the other hand, a drug that goes through the approval process is considered unsafe until the sponsor proves it to be safe. The comment concluded that, "given this scenario, a company may conclude that it doesn't make business sense to expend the considerable resources necessary to prove safety (and efficacy) for new label claims." Other comments suggested that the agency should create incentives for drug manufacturers to submit new animal drug applications (NADA's), for example, by revising the approval requirements.

The agency recognizes the need for increased availability for animal drugs and has provided for such availability as allowed under the AMDUCA in these regulations. In addition, as indicated above, recent legislation the Animal Drug Availability Act of 1996 has been enacted to increase the availability of approved animal drugs. The legislative history indicates Congress' concern about the availability of approved drugs and discussed its intention to deal with the drug availability issue separately. With regard to the "double standard" comment, the regulation does not create

the standard but merely implements the statute that allows veterinarians, under regulations issued by FDA, to prescribe drugs for animals that have not undergone the full complement of studies required for the approval process. The changes requested are not within the scope of this rulemaking.

(5) The agency asked for comment with respect to a policy that would allow or encourage sponsors to provide extralabel drug use information, regarding significant adverse events, on product labeling. A number of comments supported the inclusion of information on significant adverse events related to extralabel use on a drug's labeling. The agency is continuing to explore its legal and policy options in this regard and will consider these comments during that process. Several related comments suggested that FDA should provide more publicity on the need to report adverse reactions related to extralabel use, through the existing reporting procedures for reporting adverse drug events. FDA's Center for Veterinary Medicine (CVM) has developed and distributed widely a brochure which answers a number of frequently asked questions about CVM's adverse drug experience (ADE) reporting system. The brochure specifically addresses reporting of extralabel use-associated ADE's. CVM will take other similar proactive measures as resources permit.

2. General Comments

(6) One comment suggested that although CPG 7125.06 makes a distinction between extralabel drug use in food animals versus companion animals, the proposed regulations do not appear to make this distinction. The agency believes that the regulations clearly distinguish between the extralabel requirements for food-producing animals and companion animals, and that the differences are extensive; that is part 530, subpart C contains detailed and specific provisions relating to extralabel drug use in animals intended to provide human food. On the other hand, part 530, subpart D provides minimal conditions related to extralabel drug use in animals not intended for human consumption.

(7) One comment suggested that target animal safety should be an important consideration when prescribing extralabel use of a drug. The comment suggested that the target animal safety profile of a drug should be established so that the animal being treated is not unduly exposed to risk. While considerations of target animal safety are not specifically addressed in the AMDUCA, as is food safety, the agency

believes that the veterinarian is responsible for exercising professional judgment regarding animal safety in prescribing extralabel drug use. For that reason, both the CPG and the final rule require a valid veterinary-client-patient relationship to ensure that animal safety is properly taken into consideration. Therefore, the agency has not conditioned extralabel drug use on the establishment of a safety profile for the target animal.

(8) Several comments questioned FDA's conclusion that the AMDUCA does not permit the agency to restrict use of a human drug in nonfood animals even though an approved NAD may exist for the same uses. One comment pointed out that the agency found authority in the act to require use of an approved NAD in a food-producing animal before use of a human drug is permitted, and the comment argued that the agency could use the same authority to provide a similar restriction for drug use in nonfood animals. The comment stated that it would be prudent for FDA to do so to protect the safety of the target animal, because an approved NAD will bear labeling for the safe use of the NAD in the target animal, while a human drug will not have such labeling. Several comments noted that restricting use of a human drug in nonfood animals will maintain an important incentive for animal drug sponsors to pursue such approvals, especially in minor species. One comment stated that FDA's economic impact analysis does not consider the impact on small animal drug companies of allowing use of human drugs when approved animal drugs are available.

As stated in the preamble to the proposed rule, the AMDUCA's human drug provisions do not contain an express provision similar to the one that requires use of an approved animal drug as a prerequisite to extralabel use of another approved animal drug. The agency reiterates its belief that because of the broad public health implications in the treatment of food animals, it is prudent to require the use of an approved NAD if one exists. Because such broad public health implications do not apply to nonfood animals, the agency does not believe the statute supports a similar restriction for nonfood animals.

With regard to the comment concerning the economic impact analysis, the requirement that the agency analyze a proposal's economic impacts on small businesses is intended to disclose the economic burden that would be imposed on small business by the imposition of a new government regulation. Because FDA's analysis of

the rule's impacts concludes with a certification that it will not have a significant economic impact on a substantial number of small entities, no further analysis is required.

(9) One comment, from AHI, advocated that FDA vigorously enforce the new regulations. A number of other comments, mostly from veterinarians' groups, indicated that enforcement against extralabel drug use should be minimal. A number of comments asked how specific provisions of the regulations would be enforced.

The agency expects that its enforcement activities related to extralabel use outside the scope of the statute will continue at approximately the same level as actions under the CPG's in the past. As in the past, the agency expects to identify areas for highest priority enforcement attention, such as prohibited uses and situations in which violative drug residue occurs in human food. Enforcement instructions to FDA's field offices will be available as they are developed in the future.

(10) A number of State and university wildlife departments asked that use of drugs in free-ranging wildlife be exempted from the AMDUCA (i.e., be allowed unrestricted extralabel use) because free-ranging feral animals are not generally classified as food animals, and because it is generally impractical to maintain the veterinary-client-patient relationship provided for in the regulation. Several comments also asked that wildlife biologists be allowed to make extralabel uses because veterinarians are not always available.

The agency understands that some free-ranging wildlife may be harvested for human food, and therefore they are considered to be food animals. Accordingly, extralabel drug use in such animals must be in conformity with the provisions of the regulation applicable to food animals. In addition, the agency believes that the timing of extralabel drug use should take into consideration periods of harvest (e.g., hunting seasons). The provisions of the regulation related to nonfood animals would apply to free-ranging wildlife that are not harvested for human food. The agency recognizes the unique applicability of the veterinary-client-patient relationship to free-ranging wildlife. The agency believes that Congress intended that veterinarians be responsible for overseeing the extralabel use of drugs. However, the agency also recognizes the significant role of wildlife biologists, typically State or Federal employees, in administering drugs to free-ranging wildlife under the general supervision of a veterinarian

who may also be a government employee and intends that such situations fall within the scope of a valid veterinary-client-patient relationship. In view of the above, the agency believes that changes to the regulations are not necessary.

(11) One comment requested confirmation from the agency that it will not delay approvals or withdraw approvals of existing NADA's, if analytical methods are not developed for detection of extralabel use. It is not the intention of the agency to delay approval of a NADA, or take action to withdraw an approved NADA, if such methods are not developed. The agency notes, however, that section 512(e)(1) of the act, as amended by the AMDUCA, provides for withdrawal of an approval of a drug as unsafe under the condition of extralabel use as authorized under section 512(a)(4)(A).

(12) One comment questioned the economic assessment on two bases: (1) Whether the costs of method development included the cost of method validation, and (2) whether the assessment included the cost of developing toxicology data in order to establish a safe level. Methods validation costs, which would range from \$20,000 to \$40,000 for each trial, were not included in the cost estimates in the proposal's economic assessment. Thus, the total cost for developing a method would range from \$110,000 to \$390,000, with an intermediate level of about \$200,000 for each study. Assuming that two methods would be developed during an average year, and that one method would require a metabolism study costing \$100,000, the annual cost impact would be \$500,000 rather than \$440,000 as estimated in the proposal. This comparatively small increase in estimated costs does not materially affect the conclusions of the economic assessment under Executive Order 12866 and the Regulatory Flexibility Act. The agency does not expect to require the development of new toxicology data in order to establish a safe level, but may rely on available data for that purpose.

(13) One comment suggested that one means of reducing the risks to public health attributed to extralabel use of drugs in animals is for the agency to proactively determine, through use of a prioritized list, the extralabel use of drugs that may cause a higher risk. The comment suggested that the regulations contain provisions for developing methods, conducting tissue residue studies, and assessing toxicity of those drugs considered most likely to present public health concerns.

FDA agrees with this comment, and believes that the AMDUCA and the final regulations essentially conform to the comment's request. The agency will continuously evaluate information relating to extralabel uses. If FDA should have concerns regarding a particular extralabel use (i.e., if the agency finds that there is "a reasonable probability that a drug's use may present a risk"), the agency may establish a safe residue level or require the development of a practical analytical method. This decision would be reached by assessing toxicity data, among other information. Similarly, FDA may take additional actions if the agency finds that an extralabel use "may present a risk" or "presents a risk." The effect of this procedure would be to establish FDA's "priority list," as requested in the comment. Accordingly, the agency believes that it is unnecessary to revise the regulations.

(14) Comments from several organizations and individuals stated strong concern about the implications of extralabel use for the development and transfer of antimicrobial resistance. In general, the comments asserted that extralabel use in food animals can increase risk of drug resistance to human pathogens because studies show that antimicrobial resistance can be transmitted to humans through consumption of animal products and through contact with livestock; extralabel uses of drugs in food and water ("environmental uses") should be prohibited; extralabel use of fluoroquinolones and glycopeptides (such as vancomycin) should be prohibited; and antimicrobials approved only for use in humans should not be permitted for extralabel use in food animals. One comment also suggested prohibiting herd or flock treatment, when only a few animals exhibit symptoms.

Specifically, the Centers for Disease Control and Prevention (CDC) stated that the proposed rule does not provide adequate public health safeguards to prevent the emergence of antimicrobial resistance to agents that are important in human medicine. CDC stated that the use of antimicrobial agents in animals presents a risk to the public health as defined in the proposed rule, and noted that the proposed rule does not address the hazard caused by use of antimicrobials at low doses and for prolonged periods. CDC proposed that the extralabel use of antimicrobials be based on the results of culture and sensitivity testing, and that more stringent criteria should be applied to the extralabel use of antimicrobial drugs that are approved only for human use

including approval for such use only on a compassionate basis. CDC also commended CVM for its commitment to safeguards for the prevention of increased antimicrobial resistance including CVM's establishment and continued sponsorship of the collaborative FDA, CDC, and U.S. Department of Agriculture's (USDA's) National Antimicrobial Resistance Monitoring System.

The Center for Science in the Public Interest (CSPI) stated that CVM has acknowledged that bacteria resistant to fluoroquinolones could emerge even in therapeutic uses of the drugs, that cross-resistance occurs in the drugs, and that extralabel use of fluoroquinolones will be restricted. CSPI also recommended that subtherapeutic extralabel use be prohibited in aquaculture. The current chair of FDA's Anti-Infective Drugs Advisory Committee and of the Antimicrobial Use and Clinical Trials Committee for Infectious Disease Society of America commented that recent presentations have suggested that less drug usage can result in a reduction of resistance. That comment, and several others, referred to general recommendations that have been made to the medical profession for prudent use of antimicrobials to reduce resistance.

The agency has spent many years studying the effect of antimicrobial drug use in animals on the selection of resistant bacteria and acknowledges the concerns expressed for the public health. The agency believes that several factors will provide the basis to adequately safeguard the public health: (1) Responsible therapeutic drug use by veterinarians, as described in this regulation; (2) provisions for adequate recordkeeping, including the requirement for specifying dose and duration of treatment; and (3) resistance monitoring efforts. FDA, CDC, and USDA have implemented a national surveillance program to monitor changes in antimicrobial susceptibilities of zoonotic pathogens from human and animal clinical specimens, from healthy farm animals, and from carcasses of food-producing animals at slaughter plants. This has been done in response to recommendations from a 1994 joint FDA advisory committee meeting regarding fluoroquinolones as well as a 1995 American Society for Microbiology Task Force on Antibiotic Resistance. The monitoring system will provide descriptive data on the extent and temporal trends of antimicrobial susceptibility in *Salmonella* from the human and animal populations. The goals are to use the information in a timely way to: (1) Guide veterinarians

and physicians; (2) prolong the lifespan of drugs that are approved; (3) facilitate the identification of resistance in either population as they arise; and (4) identify areas for more detailed investigation by the appropriate group. Moreover, the monitoring system will provide direction to initiate studies designed to answer some of the more vexing scientific questions regarding the resistance issue. The early identification of emerging resistance will allow agencies to focus educational efforts in the human and veterinary medical communities on the appropriate use of antimicrobial agents.

The agency believes that the selection of resistant human pathogens could be a basis for restricting extralabel drug use provided that these organisms can be shown to present a risk to the public health. The agency will allow extralabel use of drugs administered in drinking water only for therapeutic purposes, and information on resistance will be evaluated in relation to individual drugs and classes of drugs that might be administered by this means. Subtherapeutic use of drugs in animals is typically accomplished by adding drugs to feed at a low dose and over a long-term period. Such uses are ordinarily for nontherapeutic or production purposes. As explained elsewhere extralabel use of drugs in feeds and for production purposes are not allowed under the AMDUCA. Therefore, this should not be a factor in any resistance issues arising from extralabel drug use.

The agency has decided to initiate the process specified by the AMDUCA to prohibit extralabel use of approved fluoroquinolones and glycopeptides, for animal or human use, in food producing animals. An order to this effect will be published in the Federal Register, in the near future. The agency does not have information that meets the statutory requirement (that such extralabel use presents a risk to the public health) for across-the-board prohibition of the extralabel use of antimicrobial drugs that are approved only for use in humans. The agency has not determined what, if any, authority it has to require sensitivity testing but the agency believes that such testing is part of the responsible practice of veterinary medicine. Finally, as to treatments of groups of animals when only a few are sick, the agency believes that this is not likely to occur because of cost considerations.

(15) One comment suggested that the agency needs to expand the scope of the regulations to include environmental concerns, and animal health and well-being, as well as human health. The

agency agrees that environmental and animal well-being are included in the term "public health," and intends to interpret the term broadly in making determinations under this regulation. Of course, consistent with the language of the AMDUCA and the underlying purposes of the act, the major public health consideration is human health.

(16) One comment requested that extralabel drug use criteria and precautions address environmental safety questions. The agency believes that veterinarians should take environmental impacts into account when they make an extralabel use of an animal drug. They are expected to comply with any applicable Federal or local requirements, and to report environmental problems to CVM through the ADE reporting system.

(17) One comment suggested that the regulations be modified to suggest that good management practice, preventative health management plans, and quality assurance programs be used to minimize the need for extralabel (and routine) drug use in livestock systems. The agency agrees that these are important steps in minimizing risk to the public associated with extralabel drug use in food animals. However, the agency does not believe the regulations need to be modified because these measures are part of normal veterinary and animal management practices.

3. Comments on Specific Sections

a. Scope (§ 530.1)

(18) One comment, apparently assuming that the regulations apply only to OTC drugs and expressing concern about illegal OTC sale of prescription drugs directly to farmers, suggested that the regulations should apply to veterinary prescription drugs. The agency confirms that the regulations apply to all approved drugs, whether prescription or OTC. OTC sale of prescription drugs is illegal under the act, and that status is not changed in any way by the enactment of the AMDUCA or the publication of this regulation.

b. Purpose (§ 530.2)

(19) One comment suggested that the proposed regulation's stated purpose did not adequately recognize the importance of minimizing animal pain and suffering in permitting extra-label use. The agency considers the clause "when the health of animals is threatened," in § 530.2, to include the concept of minimizing animal pain and suffering.

c. Definitions (§ 530.3)

(20) One comment stated that the regulations do not define the term "food producing animal," and asked if this

term would include species that are used for food in other countries but not in the United States. As an example the comments cited horses that are to be exported from the United States for food. Another comment suggested that the definition of food-producing animals should not include food-producing animals that are in early life stages. Another comment stated that dairy heifer calves should be considered nonfood, since they will not be used to produce food (milk) for 2 years. The agency has not defined the term "food-producing animal" in the regulation because its meaning (i.e., those animals that are intended to provide food for human consumption) is the same for purposes of this rule as it is for any other purpose under the act. Thus, horses may be food or nonfood animals, depending on their intended use. If they are intended to be exported for human consumption, they would be considered to be food-producing animals. Further, the agency does not ordinarily distinguish food-producing from nonfood-producing animals based on life-stages or production classes.

(21) One comment suggested that the term "drug sponsor" be defined. The terms "drug sponsor" and "sponsor" are used to refer to the person who holds the approved NADA. We have not provided a definition of "drug sponsor" or "sponsor" in § 530.3, because these terms are not used in the regulations in new part 530.

(22) A number of comments requested clarification of the phrase "adverse event" as used in the definitions of risk to the public health (§ 530.3(c), (d), and (e)). One comment suggested defining the term in relation to the preservation of animal health, while recognizing any science-based risk to the public health. One comment suggested that the term "adverse event" be replaced by "adverse public health event." Another comment suggested that the interpretation of "adverse event" was too narrow when confined to those events currently considered reportable adverse drug reactions required by 21 CFR 510.300 and 510.301. The agency's use of the phrase "adverse events" in these sections is related to the public health. As explained above, the agency intends to interpret the term "public health" to include animal and environmental safety in addition to human health. The agency did not intend for the term "adverse event" to be interpreted as related only to animal "adverse drug reactions." In fact, the primary focus will be on human health.

(23) One comment concluded that the description of the agency's means of determining risk as defined in

§ 530.3(c), (d), and (e) suggested that one agency's employee would make this decision or recommendation. The comment suggested that the agency involve FDA's Veterinary Medicine Advisory Committee (VMAC) in making risk determinations. Several comments proposed that the agency have defined and open processes for determining whether the statutory criteria are met. Many comments requested that the definition of these terms incorporate the concept that the determinations would be based on documented or reliable scientific information. Several comments suggested that the thresholds be more rigorous, e.g., "may be likely to cause," "may cause," and "has a direct causative link" to an adverse public health consequence, respectively, for § 530.3(c), (d), and (e). Several comments insisted that FDA was applying a double standard, i.e., by holding veterinarians to strict scientific requirements (see § 530.20) while requiring only minimal scientific information in making the threshold findings.

It was not the intention of the agency to suggest that decisions would be made by an FDA employee. Any decision regarding the risk to the public health would be an agency decision made by the appropriate agency official acting under the authority of Secretary as delegated or redelegated under the act.

FDA will consider seeking advice from VMAC, as appropriate, on issues relating to the implementation of the AMDUCA. As explained elsewhere in the preamble, and as reflected in the regulations, the agency will use defined processes, provide opportunity for public comment, and provide for public information on its risk determinations. FDA believes that the risk determinations, especially the determination that leads to prohibition of a particular extralabel use, typically will involve documented scientific information. However, the agency believes that it is not limited to making risk determinations based solely on documented scientific information, but may use other suitable information as appropriate. Finally, the agency believes that its interpretations of the statutory criteria in § 530.3(c), (d), and (e) are consistent with the plain meaning of the words, past agency interpretations of similar words, and the overall congressional purpose, and therefore has not adopted the suggested changes to § 530.3(c), (d), and (e).

With regard to the "double standard" comment, the agency believes that both the requirements for threshold determinations and those for veterinarian use of extralabel drugs in

food animals are consistent with the AMDUCA and the agency's responsibility to protect the public health.

(24) Some comments sought clarification of the term "safe level." For example, one comment asked for clarification of the third sentence in proposed § 530.3(g), which distinguishes "safe level" from other concepts such as "safe concentration" and "tolerance." The latter two terms are applied to approved drugs. A "safe level" within the meaning of the AMDUCA is one that presents essentially no human food safety concern.

(25) Several comments suggested adding the word "edible" before "animal tissues" in the first sentence of § 530.3(g). The agency agrees, and it has made the change.

(26) Many comments suggested that the definition provided in proposed § 530.3(h) for "veterinarian" and "veterinary-client-patient relationship" was adequate for individual practitioners, but needed to be amended to provide for group practices, in which several veterinarians may provide for the veterinary needs of an individual client or patient. The agency agrees with this comment, and it will interpret the regulation accordingly.

(27) Comments stated that graduation from an accredited institution should not be a prerequisite for a veterinarian to make extralabel uses, as stated in the preamble. The agency agrees, but no change is required in the regulation because the regulation did not state an accreditation requirement.

(28) One comment suggested that the veterinarian is responsible for determining the appropriate timeliness of visits, a concept that is included in the definition of veterinary-client-patient relationship in § 530.3(h). The agency agrees that timeliness is ordinarily determined by generally accepted standards of veterinary medicine practice, and it has not specified a timeliness standard in the regulation.

d. Advertising and promotion (§ 530.4)

(29) Several comments suggested that the section of the regulation prohibiting advertising and promotion of extralabel uses, § 530.4, be modified to permit the mere listing of human labeled drug products in price sheets and catalogs that are distributed to veterinarians. The agency agrees that this practice is acceptable because we do not consider mere listing of human labeled drug products in price sheets and catalogs distributed to veterinarians to be advertising and promotion of extralabel

use. However, the agency does not believe that it is necessary to modify the regulation as suggested.

e. Records (§ 530.5)

(30) Approximately two dozen organizations and individuals expressed objection to one or more provisions of the section related to recordkeeping and access to records. Only one comment favored the provision. The comment suggested a uniform Federal requirement and additional records besides those specified in the regulations, including dates of administration and use of a form specified by FDA. Generally, the comments characterized the requirement as confusing, excessive, and burdensome. The comments stated that notwithstanding FDA's preamble statement to the contrary, States do not uniformly require the records listed in the proposed regulation; in fact, the comments asserted, some States have no recordkeeping requirements at all. Several comments said, in contrast, that veterinarians keep and are encouraged to keep adequate records in accordance with generally accepted standards of practice and AVMA Guidelines for Prescription Drugs. The comments also stated that FDA should not mandate recordkeeping; the agency should specify the records that are directly related to extralabel use and access should be limited to those records; inspection should be preceded by procedural restrictions (e.g., an open process for determining when the statutory threshold of "may present a risk to the public health" is met, along with evidence that a particular veterinarian is engaged in the extralabel use in question before records are requested); and client confidentiality should be respected under State confidentiality laws. In addition, comments questioned FDA's use of the records as an enforcement tool.

FDA acknowledges that the comments are correct in their assertion that not all States require the records listed in the proposed regulation. The agency wishes to clarify the main purpose of records inspection, that is, to ascertain the extent and nature of an extralabel use that the agency has determined may present a risk to the public health information gathered in the inspection may lead to prohibition of the particular extralabel use. The main purpose of the inspection, therefore, is not enforcement of these regulations as apparently understood by the comments. The agency believes that most veterinarians keep records that would be adequate for FDA's information-gathering purposes, whether by State law or standard veterinary practice. Such records would

include identification of the drug, condition treated, species, dosage, duration, number of animals treated, and withdrawal time. However, the agency has concluded that it should specify minimal recordkeeping requirements in order to accomplish the purposes of the act. Congress has clearly provided authority for such requirement.

The agency emphasizes that the requirement to keep the records applies only to extralabel uses, and the records access provisions apply only after the agency has determined that a particular use may present a risk to the public health. As discussed in response to the next comment, the agency will give public notice of such determinations.

The agency will consider a system using notification and appointments when it develops its procedures for records inspections. The agency's personnel who collect and review records will be instructed to protect client confidentiality. As suggested by one comment, veterinarians will be allowed to copy or reformulate records to provide inspectors with only information required by the regulations.

The regulation has been modified in accordance with this discussion.

(31) A number of comments suggested that FDA give public notification of a "determination" that an extralabel use in animals "may present a risk to the public health," and that such notice be provided prior to initiating record inspections related to the particular use. The agency will provide informal public notification (e.g., articles or notices in the *CVM Update* or on the *CVM Homepage* (<http://www.cvm.fda.gov>) on the Internet World Wide Web) when it has determined that a particular use "may present a risk to the public health." It is likely that in most cases, this informal public notification will be prior to FDA initiating inspections of veterinarian records related to a particular use.

f. Feed use drugs (§ 530.11(b))

(32) Several comments addressed the provision of the AMDUCA (Section 4(a)) and the regulation, § 530.11(b), that prohibits extralabel use of a drug "in or on an animal feed." The American Feed Industry Association commented that the proposed regulation is correct, that it would clearly prohibit—without limitation or exception—the extralabel use of drugs administered in or on feed. The National Grain and Feed Association strongly supported the prohibition. Comments from organizations representing aquaculture, pheasant growers, and wildlife interests requested exceptions for their species. These groups contended, for example,

that extralabel uses should be permitted of medicated feeds that are properly formulated and labeled in accordance with regulations. Several groups suggested that there should be exceptions for use of feed to administer drugs to individual animals.

FDA believes that the act as amended by the AMDUCA does not allow extralabel use of a feed use drug (Type A article) in medicated feed or an extralabel use of the medicated feed. As stated earlier, the agency anticipates examining extralabel use which is outside the scope of AMDUCA in the context of determining regulatory priorities. In this regard, the agency notes that in the past, as a matter of enforcement discretion, the agency generally has not objected to mixing a drug with an individual animal's feed, and does not expect to change its regulatory priorities in this regard.

g. Labeling (§ 530.12)

(33) One comment sought clarification of the agency's intention, as stated in the preamble discussion of § 530.12, to allow labeling of case quantities of drugs. The agency believes case-labeling is appropriate when large numbers of animals need to be treated in an extralabel manner for a short period (e.g., feedlot use).

(34) Several comments objected to the provision in § 530.12(c), which requires that labeling identify "the animal" in which the drug is to be used. The comments proposed that the regulation allow for identification of a group of animals, i.e., a herd, where appropriate. Suggestions included requiring pen number, pasture, lot number, or other defining characteristic. The agency agrees, and it has modified the regulation accordingly.

(35) One comment suggested that the labeling requirements in § 530.12(a) be modified to allow the labeling to display either the name and address of the veterinarian, or the name of the veterinarian and the name and address of the dispensing pharmacy. The comment stated that most State pharmacy acts require the name and address of the pharmacy to appear on the labeling, while the pharmacy keeps the address of the veterinarian in its files. The comment stated that in many cases, the label is too small to include both addresses. The agency agrees, and it has modified the regulation accordingly.

h. Compounding (§ 530.13)

(36) One comment suggested that rules implementing the AMDUCA should not include regulations regarding compounding. The comment suggested that the regulation merely state that the AMDUCA does not

authorize compounding from bulk drugs or unapproved drugs, and refer to separate guidance on compounding. Compounding for use in food animals raises unique concerns with respect to drug residues. The detailed regulations for extralabel use of finished products, while generally applicable to compounding, do not fully address these unique concerns.

Therefore, the agency believes that regulations specific to compounding allowed as a result of the AMDUCA are necessary.

(37) In contrast, several comments requested that CPG 608.400, "Compounding of Drugs for use in Animals," be issued under notice and comment procedures so that the entire content of CPG would be made part of the regulations. CPG's, which set out FDA's regulatory priorities are intended to provide information and guidance. Because such policies are discretionary, they are not binding either on the agency or the public and can be changed from time to time. Notice and comment rulemaking and resulting regulations, on the other hand, establish policies which have the force and effect of law. Therefore, the use of such procedures is not appropriate for CPG's. The agency notes that it followed its usual practice and published a Federal Register notice that announced the availability of the CPG (61 FR 34849, July 3, 1996) which included the entire text of the CPG and specifically provided opportunity for comment.

(38) One comment suggested that all cutaneously administered compounds (e.g., foot bath preparations) be exempted from the compounding restrictions. The agency believes that the comment may refer to the use for compounding of drug products that have not been approved. Because the AMDUCA applies only to approved drugs, the agency does not have authority in its implementing regulations to exempt extralabel use, including compounding, of unapproved drugs. If the comment intended to address compounding from approved drugs for a specific use (i.e., cutaneous administration), such compounding must be consistent with these final rules. As stated above, further detailed guidance for compounding is provided in its compounding CPG.

(39) One comment recommended that § 530.13 be modified to be consistent with § 530.20 to state that, if available, an approved animal drug must be utilized for compounding before using a human drug for compounding. The agency agrees, and it has made the appropriate modification of § 530.13. To be consistent with § 530.30, however,

the restriction will apply only to drugs compounded for use in food animals.

(40) One comment suggested that the recently issued CPG on compounding contradicts the second sentence in § 530.13(a), and that this sentence should be deleted. The sentence states that the regulations shall not be construed as permitting compounding from bulk drugs. On the other hand, the CPG states that the agency will generally exercise enforcement discretion in very limited circumstances with regard to compounding from bulk substances. The comment suggests a misunderstanding of the difference in scope and purpose between the AMDUCA and its implementing regulations, and the compounding CPG. The AMDUCA applies only to approved products, therefore, compounding from bulk drugs could not be permitted under the AMDUCA regulations. However, limited compounding from bulk substances may be subject to FDA's enforcement discretion as expressed in the CPG. Thus, the second sentence in § 530.13(a) is not in conflict with the CPG.

i. Conditions for extralabel use in food animals (§ 530.20)

(41) One comment suggested it would be appropriate to add language to § 530.20 to state that an animal owner administering an extralabel drug under a valid veterinary-client-patient relationship shall be responsible for maintaining animal identification and observing the established withdrawal periods. The agency agrees that the animal owner as well as the veterinarian has responsibility to assure that steps are taken to avoid the occurrence of unsafe drug residues. However, the agency does not believe that the regulations need to be amended to state the animal owner's responsibility because the responsibility is emphasized elsewhere, e.g., in CPG 615.200, Proper Drug Use and Residue Avoidance by Non-Veterinarians.

(42) Comments suggested that § 530.20(a) should be revised by deleting the words "and human drugs" at the end of the sentence. The comments asserted that the deletion would provide for compliance with the specific language in the AMDUCA, and would conform to the language contained in the CPG 7125.35. The agency disagrees with the suggestion, which would mean that safeguards that would be applied to extralabel use of animal drugs in food animals would not be applied when human drugs are used in food animals. The agency believes that Congress did not intend a lesser standard of protection for the public when human drugs are used in food

animals, and that the AMDUCA provides the necessary authority to apply the standards to use of human drugs.

(43) Approximately two dozen organizations and individuals commented on the provisions in § 530.20(b) that would require veterinarians to: (1) Document the medical rationale for use of a human or nonfood animal drug in food animals, and (2) if there is no published scientific information on the public health implications, determine that the animal and its food products will not enter the human food supply. A large number of comments opposed these provisions. Comments stated that the provisions would essentially preclude extralabel use in food animals and exotic animals; that the provisions are inconsistent with standards elsewhere in the regulation (e.g., "reasonable probability of risk"); and that there is no serious drug residue problem (related to extralabel use by veterinarians) to be solved. Specifically, the comments stated that: (1) The requirement for published scientific information would exclude extralabel use of some 60 therapeutic agents, now permitted by the CPG's; (2) the regulation's requirement for published scientific information is unclear; (3) the regulation places unreasonable responsibility on the veterinarian, and it may result in substandard care for food animals; and (4) the regulation contradicts the agency's past position that there are no nonfood food animals. Most of those commenting suggested deleting these provisions from the regulation. Several suggested that the scientific information should be specified to include pharmacokinetic and toxicological information and data from sources such as the Food Animal Residue Avoidance Database, sponsors, etc. in addition to peer reviewed journals. One comment suggested that the restriction on food animal use should apply only if there is scientific information that identifies a problem. Several suggested that the regulation should require a 6 months withdrawal period, instead of permanent prohibition from food use.

The agency is primarily concerned that the veterinarian have a scientific basis for an extralabel use, and is especially concerned where the veterinarian is using in a food animal a drug that is not approved for food animal use. The agency notes that the human drug CPG contains several restrictions in addition to those contained in the animal drug CPG, and that the human drug CPG states that use of human drugs in food animals is expected to be rare. Thus, the agency

believes that there is not only a rational basis but also precedential policy that applies to the provisions of § 530.20(b).

The agency believes that the rationale for restricting use of human drugs in food animals applies as well to use in food animals of drugs approved only for nonfood animals. Such drugs often contain the same active ingredients as approved human drugs. Thus, the agency expects the veterinarian to have scientific information on which to base such use, but has deleted the requirement that the data be "published." Essentially, the agency expects that the veterinarian will have a scientific basis for using in food animals a drug that is not approved in any food animal, but that scientific information could be derived from a variety of sources, and that the veterinarian's rationale will be recorded in appropriate records. Accordingly, the agency has retained in § 530.20(b)(1) of the final rule the requirement for a medical rationale (i.e., a rational basis for using the drug), but has removed from the regulation the proposed requirement for documentation.

With respect to the veterinarian's responsibility for keeping animals out of the food supply, the agency believes that this obligation can be met by informing the client of the client's responsibility not to allow an animal to enter the human food supply. The agency has revised the regulation accordingly.

With the changes described above, FDA believes that the AMDUCA regulation will not preclude the use of approved drugs that previously have been available for extralabel use. Nor does the regulation contradict the agency's general policy that certain classes of animals are food animals regardless of circumstances.

(44) One comment suggested that the requirement in § 530.20(c) for a veterinarian to "consider" the extralabel drug be clarified to state that a veterinarian must utilize an animal drug, if one is available to treat the condition. The agency agrees and has revised the language accordingly. The agency has also deleted the requirement for documenting consideration of an approved animal drug (§ 530.20(c)). In these cases, however, a veterinarian will be expected to be able, upon request, to explain and support the use of a human drug or nonfood animal drug in food animals.

j. Prohibitions for food animals (§ 530.21)

(45) A few comments suggested that § 530.21(a), (a)(2), and (b) be modified by adding the term "extralabel" prior to the word "use" to clarify the prohibition

is for the "extralabel use" of a drug. The agency agrees, and it has made the appropriate changes.

(46) One comment asked who would be responsible for conducting and paying for the development of analytical methodology for drug residue detection. The comment suggested that this research could be done by USDA and a public master file established as is presently done for minor species claims. The AMDUCA does not specify who has the responsibility for method development. Methods may be developed under a variety of scenarios. The drug sponsor, FDA, USDA, States, or a consortium of interested parties are all possible participants. The agency is willing to work in partnership with the private and public sectors to ensure that the methods are developed when needed.

(47) A number of comments suggested that the agency exceeded its authority when it proposed to allow the prohibition of extralabel-label drug use of a class of drugs. The agency disagrees. Where a class of drugs has one or more common elements that cause a particular risk, FDA believes the statute authorizes prohibition of the entire class of drugs. Examples of situations where the agency has prohibited extralabel use of a class of drugs are the sulfonamide and nitroimidazole drug classes, which are excluded from extralabel use in the animal drug CPG. One comment suggested that as safer new analogs of drugs are being developed it is inappropriate to prohibit a class of compounds. The agency agrees. If safer analogs are developed for a drug that is in a prohibited class of drugs, the agency may amend the prohibited list as appropriate.

k. Safe levels and analytical methods (§ 530.22)

(48) One comment expressed concern over the perception that the agency has in the regulations developed two standards of safety concerning human food safety in food animals, i.e., safe levels and tolerances. The comment asserted that establishment of a safe level without complete toxicology data implies that FDA is willing to accept a lower standard of safety for extralabel use of drugs in food animals. The comment recommended that safe levels should be established based on drug metabolism and toxicology data. It also stated the criteria used by FDA to establish human food safety for extralabel use should be made public. The agency notes that the AMDUCA clearly directs the agency to permit extralabel uses that have not gone through the rigors of testing provided by

the NADA process. The law directs the agency to develop regulations that provide veterinarians the latitude to practice veterinary medicine, while protecting public health. As specific criteria for establishing human food safety are developed, information relating to those criteria will be provided to the public.

The agency has also added the words "safe concentration" in addition to the word "tolerance" in §§ 530.11 and 530.22. This is because the term "safe concentration" is used in some instances to describe safe levels of approved products.

(49) Several comments questioned the appropriateness of setting a safe level on the basis of the lowest level that can be measured by a practical analytical method. The comments stated that this is not a sound scientific basis for protecting the public health. The agency notes that where a safe level cannot be established on the basis of toxicological and other scientific information, it may require the development of an analytical method having state-of-the-art residue detection capability. Such methods can be used in an empirical strategy to minimize risk, i.e., to control or limit public exposure to residues of animal drugs for which toxicological safety information is lacking. However, the agency will not establish a safe level on this basis unless it has concluded that the lowest level of measurement sufficiently protects the public health. All relevant scientific information will be reviewed before doing so.

l. Safe levels (§ 530.23)

(50) A number of comments suggested that the agency modify § 530.23(a)(1) to include the basis for the agency's finding in the notice that establishes a safe level, and that CVM should invite the public to comment before that safe level becomes final. One comment suggested that the procedure described in § 530.22 be followed. The agency agrees with the suggestion as to the basis for the finding, and it has amended § 530.23(a), accordingly. However, the agency believes that it is not necessary to have additional procedural provisions because the regulation provides an opportunity for public comment after the safe level is established. If comments received after the safe level is established bring new information to light, the agency may revoke or modify the safe level as appropriate.

m. Analytical methods (§ 530.24)

(51) On its own initiative, the agency has modified proposed § 530.24 to include a specific process for issuance of an order announcing a specific analytical method or methods for the

quantification of extralabel use drug residues above the safe levels established under § 530.22 for extralabel use of an approved human drug or an approved animal drug. This process is the same as that in § 530.23 for setting a safe level. Under the modified procedure, 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.

n. Prohibited uses (§ 530.25)

(52) One comment requested that § 530.25(h) be reworded to require FDA to publish a safe level, whenever possible, rather than prohibit an extralabel use. The regulations do not require publication of a safe level first because the statute provides the agency with flexibility through use of the word "may." It is FDA's intention, however, to consider establishing a safe level prior to prohibiting a drug's extralabel use unless the agency finds it necessary to protect public health to prohibit the extralabel use of a drug without first establishing a safe level.

The agency has also inserted a provision in § 530.25(b) that an order of prohibition may be issued if the agency determines that an analytical method cannot be established. This provision was included in § 530.21 of the proposed rule but left out of corresponding § 530.25. This would apply in situations in which the agency has determined, based on information available to it, that development of a practical method related to the particular extralabel use is not technically feasible. This determination would be subject to comment during the comment period on the prohibition order. This allows the agency to protect the public health by eliminating the time that would elapse if the agency were to follow the procedure specified in § 530.22 for requiring development of an analytical method, in cases where the agency believes that an acceptable method cannot be developed.

The agency understands that Congress expected the agency to prohibit those extralabel uses that were prohibited under the animal drug CPG, without following the prohibition procedures prescribed by the AMDUCA. For example, Senator Heflin stated, "This bill authorizes FDA to incorporate in its initial regulations the list of prohibited extralabel uses of drugs specifically listed by name in the current compliance policy guide. Any new restrictions would have to go through the procedures established in this law prior to being prohibited." (140 Congressional Record S14071 (daily ed.

October 4, 1994.) Accordingly, § 530.41 in the final regulations includes a list prohibiting extralabel uses as specified in the CPG.

o. Nonfood animal drugs (§ 530.30)

(53) A number of comments pointed out an inconsistency between the preamble statement (61 FR 25106 at 25111) and the regulation (§ 530.30(a)) regarding extralabel uses in nonfood animals of human drugs where an approved NAD exists. The agency notes that the regulation is correct, but the preamble incorrectly stated that use of human drug is not permitted if an approved NAD for such use exists, i.e., the words "or human drug" were inadvertently added to the preamble.

(54) Many comments suggested that a new § 530.30(c) be added to read "Extralabel use of a drug approved for human use is permitted in nonfood-producing animals even if there is an identical approved new animal drug." Although the agency agrees that this statement is correct, the agency does not believe that the statement is necessary in the regulation because of the broad language in § 530.30(a).

III. 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. This final rule becomes effective December 9, 1996.

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 final rule under Executive Order 12866 and the Regulatory Flexibility Act (Pub. L. 96-354) (5 U.S.C. 601 *et seq.*). 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 final rule is consistent with the regulatory philosophy and principles identified in the Executive Order. In addition, the final rule is not a significant regulatory

action as defined by the Executive Order.

Most of the requirements in this final rule have already been implemented by regulated industry, veterinarians, and pharmacists in response to the existing CPG's 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 final rule will be quite minimal. The AMDUCA was enacted to legalize extralabel use of certain approved new human and animal drugs in veterinary medicine, and to provide FDA with specific regulatory tools to assure food safety. The scant legislative history of the AMDUCA includes evidence that the AMDUCA was intended to codify policies similar to those in FDA's CPG's.

FDA is likely to require the establishment of a safe drug residue level for one to two drugs per year after the final rule becomes effective. An analytical methodology for drug residue detection may 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. In the proposal, FDA estimated the cost for development of methodologies 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. One comment to the proposal concerned the inclusion of the costs of methods validation in the above costs. FDA did not include these costs, which range from about \$20,000 to \$40,000 for each trial, in its proposal. Adding the midpoint of this range to the previous estimate of \$170,000 for a drug presenting an intermediate level of difficulty, FDA estimates methodology development costs for the final rule to be about \$200,000 for each of these drugs. The agency estimated in its proposal that the average year would see the development of two of these intermediate level drug methodologies, with one of those drugs requiring a metabolism study. FDA did not receive any comments about this estimate and retains it for use in the final rule. Thus, total cost impacts for development of two methodologies and one metabolism

study are estimated at \$500,000 per year. The agency believes that the final rule does not impose any significant new extralabel drug use recordkeeping requirements for sponsors or veterinarians that are not currently required by other sections of the act or under State veterinary practice acts, or that are not kept by veterinarians as part of customary veterinary practice.

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. The final rule, for the most part, implements existing FDA policy, and most of the requirements in this final rule have already been implemented by regulated industry, veterinarians, and pharmacists in response to the existing CPG's relating to extralabel drug use in animals and the passage of the AMDUCA, FDA guidance, and industry trade associations' recommendations. Further, because FDA estimates that only two entities will incur economic impacts annually, the agency certifies, in accordance with section 605(b) of the Regulatory Flexibility Act, that this final 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. Federalism

FDA has analyzed this final rule in accordance with the principles and criteria set forth in Executive Order 12612 and has determined that this final rule does not have sufficient federalism implications to warrant the preparation of a federalism assessment.

VII. Unfunded Mandates Act of 1995

The Unfunded Mandates Act of 1995 (Pub. L. 104-4) (2 U.S.C. 1532) requires an agency to prepare a budgetary impact statement before promulgating any rule likely to result in a Federal mandate that may result in expenditures by State, local, and tribal governments or the private sector of \$100 million or more in any 1 year. As discussed in the preamble, the final rule essentially reflects current agency policies with respect to extralabel drug use in animals and imposes minimal new Federal requirements. Because this rule will not impose a cost of \$100 million or more on any governmental entity or the private sector, no budgetary impact statement is required.

VIII. Paperwork Reduction Act of 1995

This final rule contains information collection provisions that are subject to review by the Office of Management and Budget (OMB) under the Paperwork

Reduction Act of 1995 (44 U.S.C. 3501–3520). Therefore, in accordance with 5 CFR 1320, the title, description, and the description of respondents of the information collection requirements are shown below with an estimate of the annual reporting 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.

Title: Extralabel Drug Use in Animals—Final Rule

Description: This final 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 BURDEN¹

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

¹ There are no capital or operating or maintenance costs associated with this collection.

None of the 110 comments received had an impact on the Paperwork Reduction Act requirements. As a result, OMB has waived its option to review the paperwork at the final rule stage. Therefore, the information collection provisions in the final rule are approved under OMB Control No. 0910–0325 and are effective upon publication of this document. OMB approval expires on July 31, 1999. An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

IX. Congressional Review

This rule is not a major rule for purposes of 5 U.S.C. 801 *et seq.*, Subtitle E of the Small Business Regulatory Enforcement Fairness Act of 1996 (Pub. L. 104–121). Agency reports on this final rule have been submitted to Congress and the Comptroller General as required by 5 U.S.C. 801 *et seq.*

List of Subjects in 21 CFR Part 530

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

Therefore, under the Federal Food, Drug, and Cosmetic Act, and under authority delegated to the Commissioner of Food and Drugs, Title 21 of the Code of Federal Regulations is 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.
- 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

§ 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.

§ 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).

§ 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 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.

§ 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) 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

§ 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.

§ 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 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.

§ 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.

§ 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. 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

§ 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.

§ 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.

§ 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.

§ 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 § 530.40.

§ 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 § 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.

(b) 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 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 § 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 § 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 § 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

§ 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 § 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 extralabel drug use will be codified in § 530.41.

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.

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

§ 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) Iprnidazole;
- (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 sulfaethoxypridazine).

Dated: October 22, 1996.

William B. Schultz,

Deputy Commissioner for Policy.

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