

between the use of the drugs in man or other animals. Section 507 of the act was subsequently amended several times to include streptomycin, chlortetracycline, bacitracin, chloramphenicol, and their derivatives. The law allowed the agency to issue regulations exempting drugs or classes of drugs from the batch certification requirements. Over the years, FDA issued exemption regulations for a number of antibiotics used in animal feeds, provided the involved products were in compliance with certain provisions. The exemptions are currently contained in § 510.515.

The Animal Drug Amendments of 1968 consolidated provisions of the act relating to new animal drugs (including antibiotics in section 507 of the act) into new section 512 (21 U.S.C. 360b). The agency established procedural regulations under parts 510 and 514 (21 CFR part 514) to implement this provision of the act.

Subsequent to the establishment of the exemption provisions in § 510.515, the agency came to the conclusion that batch-by-batch certification was no longer required under any circumstances to assure the safety of antibiotics. In the **Federal Register** of September 7, 1982 (47 FR 39155), the agency published regulations exempting all classes of human and animal use antibiotics from batch certification requirements based upon a finding of extremely low rejection rates for the certifiable antibiotics.

In 1988, Congress removed from the act all antibiotic certification provisions for animal drugs when it enacted the Generic Animal Drug and Patent Term Restoration Act (GADPTRA). Subsequently, the agency published a final rule on May 26, 1989 (54 FR 22741), which removed all of the certifiable antibiotic procedural regulations that then appeared in parts 510 and 514. That rule indicated that removal of the technical regulations concerning specific antibiotic drugs, such as § 510.515, which contained information about their conditions of use, would be the subject of future regulations.

Since that time, FDA has removed many drug uses and use combinations from § 510.515. The agency did this when it withdrew approval of products subject to the regulation, or when it published approval regulations for them, in part 558, subpart B, after completing their Drug Efficacy Study Implementation (DESI) finalization (see, e.g., 61 FR 35949, July 9, 1996). Consequently, a regulation that at one time contained dozens of batch certification exemption provisions now

lists only a few products and use combinations.

B. Removal of § 510.515

The purpose of § 510.515, which was to provide exemption from batch certification of certain drugs intended for use in animal feed, was rendered obsolete with the enactment of GADPTRA. Because the regulation is out dated relative to its intended purpose, the agency is proposing to remove it.

This action is not intended to have a substantive effect on any approved new animal drugs. As noted in section II.A of this document, some of the drug uses and use combinations currently listed in § 510.515 have approvals that are codified in part 558 subpart B. Therefore, these uses will not be substantively affected by removal of listings in this regulation. Other drug use combinations currently listed in § 510.515 are also listed in § 558.15, but their approvals, if any, have not been codified in part 558 subpart B. As discussed in section II.B of this document, and in the notice appearing elsewhere in this issue of the **Federal Register**, the use combinations that have been approved will be codified in part 558 subpart B. In regard to the only other listed drug (*para*-aminobenzoic acid), the agency is unaware of any company that currently holds approval for it, or markets it, and believes it is no longer used in the practice of veterinary medicine. If a person wishes to market a drug or drug combination being removed under this proposal and believes that it holds a valid approval for it that is not already codified in part 558 subpart B or subject to the final rule or notice published elsewhere in this issue of the **Federal Register**, the person should present evidence supporting approval to avoid facing potential regulatory action in the event of future marketing.

III. Section 558.15 Antibiotic, Nitrofurans, and Sulfonamide Drugs in the Feed of Animals

A. History of § 558.15

In the mid-1960s, FDA became concerned about the safety to man and animals of long-term antibiotic use in animals, and for several years the agency studied the effects of low-level feeding of antibiotics to animals. In April 1970, the Commissioner of Food and Drugs (Commissioner) established a task force of scientists from government, industry, and academia to comprehensively review the use of antibiotics in animal feed. In the **Federal Register** of February 1, 1972 (37

FR 2444), the agency published the conclusions of that task force and proposed to require sponsors to submit specific data for antibacterial drugs intended for subtherapeutic or growth promotion use. The task force identified areas in which data were needed and established criteria for studies intended to show whether use of antimicrobials in animal feed presents a hazard to human or animal health. The criteria reflected four basic issues with respect to which data were needed: (1) The potential to increase the frequency of bacteria carrying transferable drug resistance; (2) the potential to increase the antibiotic resistance of, or the shedding of, *Salmonella* spp.; (3) the potential to enhance bacterial pathogenicity; and (4) the potential for drug residues to cause an increase in pathogenic bacteria resistant to human antibiotics drugs or to cause human hypersensitivity reactions. The 1972 proposal also stated that all then-approved subtherapeutic and/or growth promoting uses in animal feeds of antibiotics and sulfonamides that are also used in humans would be revoked unless data identified by the task force were submitted to FDA.

In the **Federal Register** of April 20, 1973 (38 FR 9811), the agency published the final rule which established 21 CFR 135.109 *Antibiotic and sulfonamide drugs in the feed of animals* (redesignated as § 558.15 in 1974). The section was subsequently amended on September 5, 1973, to include the nitrofurans (38 FR 23942). In the **Federal Register** of February 25, 1976 (41 FR 8282), the agency withdrew approvals for those antimicrobial drugs not in compliance with the data submission requirements of § 558.15. The same document added paragraphs (g)(1) and (g)(2) to § 558.15. These paragraphs listed the medicated premixes and drug combinations, respectively, which had submitted the required data for agency review. These are known as the interim marketing provisions.

B. Approval Status of Products and Use Combinations Subject to the Listings in § 558.15

The preamble to the final rule that added the § 558.15 interim marketing provisions stated that all products and combination uses subject to the listings in the regulation were the subject of approved applications (41 FR 8282 and 8285, February 25, 1976). However, a number of years after this regulation was issued, it became apparent that the administrative record associated with 15 products was incomplete, calling into question their approval status.