

One cause of this problem relates to the Animal Drug Amendments of 1968. Under Section 108 of this law, any product that had been approved before 1968 by a new drug application, food additive petition, certifiable antibiotic application, or master file would be considered to be the subject of an approved new animal drug application under the new section 512. Because § 558.15 dealt with antimicrobials used in animal feed, the products listed in § 558.15 were considered food additives before the 1968 animal drug amendments. In addition, a number of them contained certifiable antibiotics. The approval processes for these products before the 1968 amendments were complex, redundant, and involved the acceptance of secondary manufacturers/distributors, sometimes based on a demonstration of equivalence of their products to primary sponsor products and sometimes not. Unlike the current new animal drug application process under section 512 of the act, this was generally not an orderly process. As a result, the agency's and sponsors' ability to document the pre-1968 approvals has been hampered.

Because their administrative records were incomplete, in 1998 the agency undertook to determine whether any of the 15 products were unapproved and, therefore, erroneously listed in § 558.15. In this regard, the agency asked sponsors to identify the involved product, attach associated labeling, and certify its approval status. Certification was forthcoming for 10 of the 15 applications. The agency informed the involved parties by letter that their certifications would be used as part of the administrative record of approval and that it planned to codify these approvals as soon as possible, very likely in concert with the removal of § 558.15. Because the agency was unable to verify that the remaining five products were approved, the agency believes they were erroneously listed in § 558.15.

#### *C. Reasons for Removal of § 558.15*

The agency is proposing to remove § 558.15 because it long ago fulfilled its stated purpose of requiring sponsors to submit data regarding the subtherapeutic use of antibiotics on the market at the time of its publication. The safety studies required to be conducted on the products listed at the time the section was issued were completed long ago. In addition, as discussed in section III.D of this document, the agency has a new strategy and concept for assessing the safety of antimicrobial new animal drugs, including subtherapeutic use of

antimicrobials in animal feed, with regard to their microbiological effects on bacteria of human health concern. Therefore, the removal of § 558.15 does not mean that studies will no longer be required to assess the consequences of the use of antimicrobials in food-producing animals.

#### *D. The Antibiotic Resistance Issue After Publication of § 558.15*

While, at the time of its publication, § 558.15 accurately reflected FDA's basis for assessing the safety of subtherapeutic uses of antibiotics in feed, based on new information and considerable experience, over time FDA developed a new strategy and concept to deal with the issue of antimicrobial resistance. Accordingly, it is useful to review the history of the antimicrobial resistance issue from the time § 558.15 was issued to the present relative to the significance of the removal of § 558.15 on FDA's ability to deal with the issue.

As discussed in section III.A of this document, under § 558.15, FDA received data addressing the subtherapeutic use of antibiotics in animal feed. To assist FDA in assessing the data, the Commissioner asked the agency's National Advisory Food and Drug Committee (NAFDC) to review the data and issues involved and to make recommendations to him on the future use of subtherapeutic antibiotics in animal feeds.

In 1977, the NAFDC made its findings known to FDA. The FDA carefully considered the recommendations made by the NAFDC. On August 30, 1977 (42 FR 43770), the Director of the Center for Veterinary Medicine (Director) proposed to revoke all regulations providing for the subtherapeutic use of penicillin alone and in combination with other drugs in animal feeds. Because the National Academy of Sciences National Research Council (NAS/NRC) DESI review concluded that no therapeutic uses of penicillin in animal feed were supported by adequate evidence of effectiveness, he also proposed to revoke all regulations providing for the therapeutic use of penicillin in animal feed. Also, in the **Federal Register** of August 30, 1977 (42 FR 43772), the Director issued a notice of opportunity for hearing (NOOH) on a proposal to withdraw approval of NADAs for all penicillin-containing premixes intended for use in animal feeds. The NOOH was issued, under section 512(e) of the act (21 U.S.C. 360b(e)), on the grounds that evidence showed that such products have not been shown to be safe, that the applicants failed to establish and maintain records and make reports as required, and that there was a lack of

substantial evidence that such products were effective for certain uses.

Subsequently, in the **Federal Register** of October 21, 1977 (42 FR 56254), the Director proposed to revoke regulations providing for the subtherapeutic use of tetracyclines in animal feed except for those specific conditions of use for which there were no safe and effective substitutes at that time. Also in the **Federal Register** of October 21, 1977 (42 FR 56264), the Director issued an NOOH on a proposal to withdraw approval of NADAs for certain subtherapeutic uses of tetracyclines (chlortetracycline and oxytetracycline) in animal feeds.

In 1978, after FDA proposed to withdraw approval of various uses of penicillin and tetracyclines in animal feeds, Congress directed FDA to conduct further studies related to the use of antibiotics in animal feed and to hold in abeyance implementation of its proposed withdrawal actions pending the outcome of the studies (see H.R. Rept. 95-1290 at p. 99 (June 13, 1978)). As directed, FDA spent \$1.5 million of its appropriations for a study of the safety issues relating to the use of antibiotics in animal feeds. The study entitled "The Effects on Human Health of Subtherapeutic Use of Antimicrobials in Animal Feeds," conducted by the NAS/NRC, was published in 1980 (Ref. 1). It concluded that existing data could neither prove nor disprove the postulated hazards to human health from subtherapeutic antimicrobial use in animal feeds.

On November 20, 1984, the Natural Resources Defense Council, Inc. (NRDC), petitioned the Secretary of Health and Human Services (Secretary) to immediately suspend approval of the subtherapeutic use of penicillin and tetracyclines in animal feeds (Ref. 2). NRDC's petition requested that the Secretary invoke the imminent hazard provision of the act (21 U.S.C. 360b(e)(1)) which authorizes the Secretary to suspend approval of an application for the use of a new animal drug if an imminent hazard exists to the health of man or to the animals for which the drug is intended. Soon after the filing of the petition, there was a congressional hearing in December 1984 before the House of Representatives Committee on Science and Technology, Subcommittee on Investigations and Oversight, as well as an informal hearing before the Commissioner of FDA on January 25, 1985.

On November 13, 1985, the Secretary denied the NRDC petition on the basis that an "imminent hazard" had not been demonstrated (Ref. 3). This decision was based on an analysis of the evidence cited by the NRDC as well as scientific