

evidence, information, and opinions coming out of the January 25, 1985, public hearing and other relevant data collected and analyzed by FDA.

Subsequently, the Commissioner directed the agency to contract with the NAS, Institute of Medicine (IOM), to conduct a risk assessment of the potential risk to human health associated with the practice of feeding subtherapeutic levels of penicillin and the tetracyclines to animals for growth promotion, feed efficiency, and disease prevention.

In 1988, the NAS/IOM reviewed the information concerning the antibiotic resistance issue available at the time. An expert committee was convened to determine the human health risks associated with the practice of feeding subtherapeutic levels of penicillin and tetracyclines to animals for growth promotion, feed efficiency, and disease prevention. In the report entitled "Human Health Risks with the Subtherapeutic Use of Penicillin or Tetracyclines in Animal Feed" the committee developed a risk-analysis model, using data only on *Salmonella* infections that resulted in human death (Ref. 4). The committee found a considerable amount of indirect evidence implicating both subtherapeutic and therapeutic use of antimicrobials as a potential human health hazard. The committee did not find data demonstrating that use of subtherapeutic penicillin or tetracycline directly caused humans to die from salmonellosis. The committee noted that it was not possible to separate the public health effects of therapeutic and subtherapeutic uses and strongly recommended further study of the issue.

Based upon the report and other relevant information, the agency: (1) Concluded that the risks were neither proved nor disproved, (2) did not deny there was some degree of risk, and (3) did not conclude that the continued subtherapeutic use of penicillin and the tetracyclines in animal feed is safe. The notices of opportunity for hearing published in the **Federal Registers** of August 30 and October 21, 1977, remain pending.

The American Society of Microbiology issued a report in 1995 that cited grave concerns about both human and animal antibiotic use and the rise in antimicrobial resistance (Ref. 5). The report advocated: A significant increase in resistance monitoring in the United States, more education about the use and risks of antimicrobials, and more basic research designed to develop new antimicrobials and vaccines and disease prevention measures. The report criticized overuse of antibacterials in

human medicine, but also pointed out the extensive use of antibacterials in food production, which was partly attributed to the consolidation of farms to facilities with large numbers of confined animals. The report made it clear that the antibiotic resistance problem is global and was a precursor to involvement by the United Nation's World Health Organization (WHO). The meetings of the WHO in 1997 and 1998 led to the development of a number of recommendations regarding the use of antimicrobial drugs in food-producing animals (Refs. 6 and 7).

In 1999, FDA issued "Guidance for Industry: Consideration of the Human Health Impact of the Microbial Effects of Antimicrobial New Animal Drugs Intended for Use in Food-Producing Animals" (#78) (64 FR 70715, Dec. 17, 1999). In this guidance, FDA reaffirmed its statutory authority to evaluate the safety of new animal drugs with respect to their microbiological effects on bacteria of human health concern. FDA asserted that this consideration applies to all antimicrobial new animal drugs intended for use in food-producing animals including both therapeutic use and use at subtherapeutic levels for production purposes. Subsequently, the agency released a concept paper, which has come to be known as the Framework Document, which described a possible approach that the FDA could take in regulating antimicrobial new animal drugs intended for use in food-producing animals (Ref. 8).

Since the publication of the Framework Document, FDA has held a number of public meetings as well as two meetings of its Veterinary Medical Advisory Committee to obtain input on the concepts outlined in the Framework Document. Based on this input, FDA drafted a guidance for industry (GFI) to implement several of the key strategies and concepts discussed in the Framework Document. The draft guidance for industry entitled "Draft Guidance for Industry: Evaluating the Safety of Antimicrobial New Animal Drugs With Regard to Their Microbiological Effects on Bacteria of Human Health Concern" (#152) (67 FR 58058, Sept. 13, 2002) outlines a risk analysis process for evaluating the safety of antimicrobial new animal drugs. This guidance, subject to public comment, represents the Center for Veterinary Medicine's current best thinking on how to assure the safety of antimicrobial new animal drugs intended for use in food-producing animals.

E. Effect of the Removal of § 558.15

Based on the previous discussion, the removal of § 558.15 will have no effect on FDA's ability to address the issue of antimicrobial resistance. Additionally, the removal of § 558.15 is not intended to have a substantive effect on the products subject to the section's interim marketing provisions. Most of the products or use combinations subject to the listings have approvals that are already codified in part 558 subpart B. The agency's actions on the products and use combinations whose approval is not already codified in part 558 subpart B are described elsewhere in this issue of the **Federal Register**. One action consists of publishing the agency's findings of effectiveness for these products and use combinations, under DESI, and, where relevant, proposing to withdraw approval of applications for indications lacking substantial evidence of effectiveness and providing a notice of opportunity for hearing. The other action is the codifying of one approval in part 558 subpart B. This action is a final rule since the product is not subject to DESI. As noted in section III.B of this document, the agency believes that five products subject to the listings in § 558.15 were erroneously listed there. Because the regulation could only permit the interim marketing of approved products, the removal of § 558.15 will not have a substantive effect on the five unapproved products. Further, the agency is unaware of any company that currently markets any of these five products. If a company wishes to market one of these drug products and believes that it holds a valid approval for it that is not already subject to an approval reflected in part 558 subpart B, the company should present evidence supporting approval to avoid facing potential regulatory action in the event of future marketing.

IV. Environmental Impact

The agency has determined under 21 CFR 25.30(h) 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 Economic Impacts

FDA has examined the impacts of the proposed rule under Executive Order 12866 and the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act of 1995 (Public Law 104–4). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory