

about the emergence of drug-resistant bacterial strains.

The final rule has been revised in response to comments received on the proposed rule. The comments and responses are discussed in section III of this document. In the final rule, the agency has significantly revised the statements required directly under the product name, in the "Indications and Usage" section, and in the "General" subsection of the "Precautions" section. The agency made minor revisions to the statement proposed for the "Information for Patients" subsection of the "Precautions" section. The final rule omits the statement that was proposed for the "Clinical Pharmacology" section.

The final rule requires that the labeling for all systemic drug products indicated to treat a bacterial infection, except a mycobacterial infection, include the following information.

At the beginning of the label, under the product name, the labeling must state that to reduce the development of drug-resistant bacteria and maintain the effectiveness of the antibacterial drug product and other antibacterial drugs, the drug product should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

In the "Indications and Usage" section, the labeling must state that to reduce the development of drug-resistant bacteria and maintain the effectiveness of the antibacterial drug product and other antibacterial drugs, the drug product should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. The labeling must state that, when culture and susceptibility information are available, they should be considered in selecting or modifying antimicrobial therapy. The labeling must also state that in the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

In the "General" subsection of the "Precautions" section, the labeling must state that prescribing the antibacterial drug product in the absence of a proven or strongly suspected bacterial infection of a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

In the "Information for patients" subsection of the "Precautions" section, the labeling must state that patients should be counseled that antibacterial drugs, including the antibacterial drug product prescribed, should only be used to treat bacterial infections and that they do not treat viral infections (e.g., the

common cold). The labeling must state that when an antibacterial drug product is prescribed to treat a bacterial infection, patients should be told that, although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. The labeling must also advise physicians to counsel patients that skipping doses or not completing the full course of therapy may: (1) Decrease the effectiveness of the immediate treatment, and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by the antibacterial drug product or other antibacterial drugs in the future.

III. Comments on the Proposed Rule

FDA received 19 comments on the proposed rule. The comments were submitted by pharmaceutical companies, trade associations, individuals, and public and private health organizations.

A. Statements of Support

(Comment 1) Many comments supported the proposed rule. One comment expressed the view that the proposal will be another step in building public awareness and improving antibiotic use before there is a public health emergency. Another comment stated that the proposed rule is an important first step in more appropriate use of antimicrobial agents by health care workers and that regulatory actions have the potential for positive impact on the problem of antibiotic resistance. Another supportive comment stated that for the label changes to have an impact, it will be important to ensure that all antimicrobial drug promotional and marketing activities, whether directed at clinicians, health care organizations, or the public, explicitly and thoroughly communicate the cautions expressed in the rule.

(Response) FDA recognizes the importance of increasing awareness by health care providers and patients about the appropriate use of antibiotics and the cautions about antibiotic resistance. FDA will work with sponsors on ways that these important messages can best be communicated.

B. Sources and Frequency of Antibiotic Resistance

(Comment 2) The agency received many comments concerning the sources of antibiotic resistance. One comment contended that the proposed labeling statements imply that inappropriate use of antibiotics is the only reason for the development of resistance, a notion with which the comment disagreed.

Another comment maintained that more likely causes of resistance than individual misuse of antibiotics are a breakdown in basic infection control practices and hygiene (e.g., hand washing, immunization, adequate personal care in daycare centers for children and adults). Another comment cited daycare, veterinary use, and improper hand washing as reasons for antibiotic resistance. This comment also stated that even if doctors prescribe appropriately, resistance to antibiotics will still occur because of selection of resistant strains arising from normal physiological spontaneous mutations.

One comment stated that the emergence of resistance involves many factors including intrinsic properties of the drug, such as whether it has a static or cidal mechanism of action and the nature of its cellular target, and extrinsic considerations, such as the target organism, the health of the patient, the type and site of infection, and prior exposure of the patient to antibiotics. Another comment stated that the proposal ignores other factors involved in minimizing resistance and determining clinical outcome. These factors include pharmacodynamic data, including information on tissue or drug concentrations at the site of infection, and host factors, such as risk for resistant bacterial infections.

(Response) FDA believes labeling concerning antibiotic resistance has the potential to make a significant contribution toward the goal of reducing resistance. The agency is aware, however, that many factors contribute to antibiotic resistance and that there need to be efforts on many fronts to combat the resistance problem. FDA's proposal does not imply that the wisest use of antibiotics by physicians would eliminate the resistance problem entirely. FDA agrees that, regardless of the measures adopted, some level of antibiotic resistance will be present because of the selection of resistant strains that arise during normal bacterial reproduction.

This final rule is one of many ongoing efforts by FDA to combat antibiotic resistance. FDA has previously and will continue to organize and participate in numerous advisory committee meetings, open public meetings, and workshops with industry and academia to focus on strategies to encourage the development of new antimicrobials while preserving the usefulness of existing drug products. Past meetings have already led to changes in the collection of clinical data by stakeholders that will ultimately shorten the development time of future antimicrobial products. The agency has an ongoing partnership with other