

government agencies and medical organizations to educate the public about the proper use of antimicrobials and the risks of inappropriate use. FDA has recently awarded a contract to a company to obtain antimicrobial resistance surveillance information in an effort to help the agency identify resistant organisms that pose a significant health threat to the public.

(Comment 3) One comment agreed that any use of antibiotics may increase selective pressure, but stated that decreased effectiveness of antibiotics is a greater clinical concern in empiric therapy when microbiological data for a particular patient are not readily available.

(Response) Existing antibiotics may become less effective because of antibiotic resistance. Thus, reducing the development of resistance and maintaining the effectiveness of existing antibiotics are intertwined goals. FDA's concern with these goals is indicated in the revised statement to appear under the product name, which advocates using antibiotics only for bacterial infections in order to reduce the development of drug-resistant bacteria and maintain the effectiveness of existing antibiotics.

(Comment 4) One comment objected to the general nature of the proposed labeling statements because certain antibiotics, for example cephalosporins, are more likely to be associated with the development of resistance than others. Another comment stated that newer antibiotics are less likely to generate resistance. The comment also stated that the differences in *in vitro* frequency of resistance in different classes of antibiotics suggest that continued research can decrease the frequency of resistance by emphasizing, in drug development, factors such as area under the curve/minimum inhibitory concentration (MIC) and maximum concentration (C_{max})/MIC ratios. Another comment maintained that there should be greater emphasis on the use of pharmacokinetic (PK) and pharmacodynamic (PD) data to provide clinically relevant information to establish which antibiotics are likely to maximize efficacy and minimize the risk of developing resistance. The comment stated that this suggestion accords with the FDA Anti-Infectives Advisory Committee's recommendation that the PK/PD relationship for antibiotics be investigated during drug development.

(Response) The final rule affects all systemic antibacterial products because all antibiotics develop resistance, even though the frequency of resistance can vary among different antibiotics. FDA

supports efforts by pharmaceutical companies to investigate PK/PD relationships during drug development. However, it would not be appropriate at this time to require PK/PD information in the labeling of antibiotic drug products. A number of factors limit the usefulness of PK/PD relationships in clinical practice. First, it has not been established that population PK/PD relationships are predictive of outcomes in individual patients. Second, there are practical obstacles to the use of this information by physicians. To make use of a PK/PD relationship, the physician would have to have access to PK information, that is the level of antibiotic in the patient's blood, and PD information, the MIC for the specific strain of bacteria. Measuring antibiotic levels in patients' blood requires specialized testing that is not available on an outpatient basis and may not even be available in hospitals. As discussed in section III.H of this document, susceptibility testing is often not performed. Even if susceptibility data were available, the information may not be provided quantitatively so that it can be used in a PK/PD ratio.

(Comment 5) One comment maintained that all antimicrobials have built-in obsolescence, and thus there will be a natural progression of selection for resistance regardless of how appropriately doctors prescribe antibiotics.

(Response) Regardless of whether all antibiotics will eventually lead to resistant bacteria, there are great benefits to delaying that progression as long as possible. As stated previously, there is a strong correlation between the improper use of antibiotics and the incidence of antibiotic drug resistance. The CDC estimates that as much as 50 percent of antibiotic use is unnecessary, that is, prescribed for diseases like the common cold that do not respond to antibacterial drugs. Judicious physician prescribing of antimicrobial agents and proper antibiotic usage by patients play an important role in slowing down the natural progression of selection for resistance to antibiotics. For example, limiting the use of erythromycin in Finland decreased the rate of resistance to this drug in group A streptococci causing sore throats by approximately 50 percent.

C. Influence of Labeling

(Comment 6) Some comments suggested that doctors will probably not be influenced by the proposed labeling. One comment stated that since doctors treat infections empirically despite advice in current labeling to determine the causative agent, it is unlikely that

the new labeling will influence doctors' behavior. One comment stated that FDA's Director of the Office of Postmarketing Drug Risk Assessment expressed the opinion that labeling changes do not alter doctors' prescribing practices. Another comment expressed the view that doctors are already aware of the information contained in the proposed labeling and therefore might be offended by the labeling or might not read the warnings. Another comment stated that it is questionable whether prescribers read package inserts thoroughly because of their length and small print. Another comment contended that before adopting the proposal, FDA should assess whether physicians understand the proposed labeling and change their behavior as a result. One comment stated that FDA should send periodic letters to prescribers giving updates on antibiotic resistance and prudent use of antibiotics because doctors may not read package inserts.

(Response) Antibiotic resistance is a serious public health problem that needs to be addressed by a major educational effort. FDA believes that physician labeling can contribute to that effort by reminding physicians that their individual prescribing decisions have a collective impact on the resistance problem. The agency believes that physicians frequently consult selected portions of the package insert and thus will encounter one or more of the statements on antibiotic resistance that appear in multiple, significant locations in the package insert. The agency believes that the prominence of the statement under the product name will be particularly likely to have an effect on prescribing decisions. FDA believes it is important to institute labeling discussing antibiotic resistance as soon as possible because it will be an important step in addressing the resistance problem; therefore, the agency declines to adopt the suggestion to measure the effect of the labeling before adopting the rule. The agency also rejects the suggestion to send "Dear Doctor" letters; the package insert, rather than letters, is FDA's primary tool for communicating with physicians.

D. Alternatives and General Comments

(Comment 7) Many comments stated that labeling is not the best way to accomplish the goal of reducing antibiotic resistance and suggested alternative mechanisms. Several comments suggested using educational and scientific forums to educate doctors. Organizations mentioned as appropriate to provide educational programs included pharmaceutical companies