

product name would detract from boxed warnings that appear at the beginning of labeling. Systemic antibacterial products rarely contain boxed warnings. Furthermore, physicians recognize that a box demarcates a critical warning; therefore, placement of a statement before the boxed warning would not detract from that warning.

The agency disagrees with the claim that placing a statement under the product name conflicts with § 201.57(e). That section does not state that the only information that can be placed directly under the product name is a boxed warning. Nor does the section state that boxed warnings must be placed directly under the product name. Section 201.57(e) states: "If a boxed warning is required, its location will be specified by the Food and Drug Administration." It should be noted that boxed warnings may appear anywhere in the package insert, not only under the product name.

(Comment 21) One comment objected to placement of the statement under the product name because the same statement appears in the "Precautions" section.

(Response) In the final rule, the statements for both locations have been revised, and two different statements now appear in these two sections.

(Comment 22) One comment opposed the proposal but stated that if the agency were to proceed with it, a statement concerning antimicrobial resistance should be in a new section entitled "General," which would appear before one of the existing sections of labeling that doctors are likely to read such as "Microbiology," "Indications and Usage," or "Dosage and Administration." Another comment stated that of the two locations proposed for a general statement on antibiotic resistance, the "Precautions" section is a more suitable place for such a statement than directly under the product name.

(Response) FDA believes that the labeling statements required by this final rule are appropriately placed to be as visible as possible to readers; therefore, the agency declines to adopt the suggestion to create a new labeling section entitled "General" or to adopt the suggestion not to require a statement under the product name.

(Comment 23) Three identical comments stated that all anti-infective labeling should contain a new section entitled "Clinical Microbiology" because physicians and nurses are used to seeing clinical microbiology information under that heading rather than under "Clinical Pharmacology." The comments maintained that the statement proposed for the "Clinical

Pharmacology" section appear instead in this new section because the statement is more correctly a "Clinical Microbiology" statement rather than a "Clinical Pharmacology" statement. The comments also stated that readers would recognize the statement more easily if it were in a separate section. Another comment stated that the language proposed for the "Clinical Pharmacology" section should appear in a "Microbiology" subsection of the "Clinical Pharmacology" section, adding that this type of information does not belong in any other area of the "Clinical Pharmacology" section. Another comment stated that the "Clinical Pharmacology" section should also include a summary of the preclinical and clinical data regarding PK and PD parameters to predict clinical response and minimize development of resistance, but that if such data are lacking, that should be stated.

(Response) The agency has decided that advice about obtaining cultures belongs in the "Indications and Usage" section rather than the "Clinical Pharmacology" section. Because the rule does not require microbiology information, there is no need for a separate microbiology section.

(Comment 24) Two comments stated that the proposal contradicted approved labeling for prophylaxis indications. One comment stated that antibiotic use for prophylaxis is within the standard of care and is found in indications in several labels (i.e., mezlocillin, cefuroxime, and metronidazole). Another comment noted that antibiotic use for prophylaxis of bacterial infection in some settings is an FDA-approved and valuable clinical use of several antibacterial drugs. Another comment stated that the "proposed statements deviate from the long-standing practice of FDA to grant indications for each specific infection that was studied in adequate and well-controlled trials."

(Response) FDA recognizes that some antibacterial drug products are indicated for prophylactic use, for example, to prevent postoperative bacterial infection. The statements required by the final rule to appear under the product name and in the "Indications and Usage" section advise that antibacterial drug products "should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria." The statement required in the "Precautions" section, under the "General" subsection, also recognizes that some antibacterial drug products are indicated for prophylaxis. The final rule has no

impact on the approval of antibiotics for various indications.

G. Statements Under the Product Name and in the "Precautions" Section

The proposed rule would have required that the following statement appear directly under the product name and also in the "Precautions" section:

Inappropriate use of (*insert name of antibacterial drug product*) may increase the prevalence of drug resistant microorganisms and may decrease the effectiveness of (*insert name of antibacterial drug product*) and related antimicrobial agents.

Use (*insert name of antibacterial drug product*) only to treat infections that are proven or strongly suspected to be caused by susceptible microorganisms. See Indications and Usage section.

This statement used the term "inappropriate use" of antibacterial drug products.

(Comment 25) Several comments objected to the term "inappropriate use" as vague and subject to varying interpretations. One comment asked that inappropriate use be defined. Another comment maintained that the rule should focus on appropriate, rather than inappropriate, prescribing and should include a clear definition of appropriate prescribing. This comment asserted that it is important to distinguish between unnecessary use, such as prescribing an antibiotic for a viral infection, and inappropriate use, such as prescribing antibiotics at the wrong dose or for the wrong duration, or prescribing the wrong antibiotic to treat a particular bacterial infection. The comment also maintained that it is entirely appropriate to prescribe antibiotics whenever a bacterial infection is suspected, even in patients who initially have influenza-like symptoms.

The comment also stated that a definition of appropriate prescribing should include the following points: (1) There must be a known or suspected bacterial infection, and (2) the choice of antibiotic should effect a rapid inhibition of bacterial growth, ideally by bacterial kill, and minimize the development of resistance and drug-related toxicity. This comment also stated that failure to use antibiotics may lead to serious bacterial infections that progress, and that the proposed rule's focus on inappropriate use might have the unwanted result of making doctors hesitate to prescribe antibiotics when they are truly necessary to treat a bacterial infection. One comment expressed the opinion that when a doctor uses his judgment about prescribing, that is not inappropriate use. Another comment stated that appropriate use of antibiotics may also