

comment suggested that FDA propose another rule that would cover antimycobacterials, topical antibiotics, and antiseptics. Another comment stated that the proposal should cover topical products because they are sometimes an alternative to systemic antibacterials. Another comment questioned the exclusion of drugs to treat tuberculosis. Another comment anticipated that statements concerning antibiotic resistance will eventually be included in the labels of antiparasitic, antiviral, antifungal, and antimycobacterial agents, topical antibacterials, and topical antiseptics. This comment recognized that labeling for these products involves unique challenges, but expressed the view that development of resistance to these types of agents is a real or potential problem that may be aggravated by inappropriate use.

(Response) Prescription and OTC topical antibacterials, topical antiseptics, antimycobacterial drugs, and veterinary antibiotics raise different scientific and regulatory issues than do systemic antibacterials. The agency is considering how to address concerns about the development of antibiotic resistance from the use of these other types of products and will consider whether additional rulemaking would be appropriate.

(Comment 16) A few comments requested clarification of the scope of the proposed rule. One comment asked if the rule would apply to oral antibiotics or intravenous (IV) antibiotics, or both. Another comment asked whether the proposal would apply to antibiotics such as clarithromycin and rifampin that are used for mycobacterial infections as well as for regular bacterial infections.

(Response) The final rule applies to both oral and IV antibiotics. The final rule applies to all systemic antibacterials that are indicated for the treatment of bacterial infections, even if, like clarithromycin and rifampin, they are also indicated for the treatment of mycobacterial infections.

(Comment 17) One comment stated that generic antibiotics should be held to the same standard as innovator products. Another comment asserted that labeling that has already been approved should be grandfathered, and the rule should not apply to it. Another comment stated that the rule's effective date should be contingent on complete implementation of the surveillance, prevention, and control goals identified in the joint CDC, FDA, and National Institutes of Health "Draft Public Health Action Plan to Combat Antimicrobial

Resistance" (65 FR 38832, June 22, 2000).

(Response) The final rule applies to both generic and branded systemic antibacterial drug products. FDA declines to adopt the suggestion that the rule not apply to already-approved labeling because there is no scientific basis to distinguish between products approved before the effective date of the rule and products approved after the effective date in terms of causing antibiotic resistance. The agency believes it is important to implement the final rule as soon as possible and therefore rejects the notion that the effective date should be delayed to coordinate the rule with other items in the June 22, 2000, Action Plan.

F. Location of Statements

(Comment 18) Many comments expressed the view that requiring statements in five locations in the labeling would be redundant. One such comment stated that the repetitiveness would clutter the label without adding value. Another comment contended that the redundancy of the warnings would cause doctors to view them as "boilerplate noise." Another comment pointed out that the same statement appears under the product name and in the "Precautions" section. Another comment stated that the statements in the "Clinical Pharmacology" section and the "Indications and Usage" section are redundant.

(Response) In response to these comments, FDA has eliminated the statement proposed for the "Clinical Pharmacology" section. In addition, the same statement does not appear under the product name and in the "Precautions" section in the final rule; the statements for these locations have been revised. As discussed in the response to comment 6 in section III.C of this document, FDA recognizes that physicians are unlikely to read the package insert in its entirety whenever they prescribe an antibiotic. Instead, physicians consult selected portions of the package insert. The agency's intent in requiring warnings directly under the product name and in the "Indications and Usage" and "Precautions" sections was to ensure that most physicians will encounter one of the statements on antibiotic resistance when they are considering whether to prescribe an antibiotic.

In addition, the context and wording of each of the four statements is different. The statement under the product name emphasizes that the goal of reducing the development of drug-resistant bacteria and maintaining the effectiveness of antibacterial drugs can

be accomplished by using antibacterials only to treat infections that are proven or strongly suspected to be caused by bacteria. The statement in the "Precautions" section warns that prescribing antibacterials other than to treat a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient. The "Indications and Usage" section is where the physician looks to see what the uses of the product are. It is the most frequently consulted portion of the labeling. The statement in this section advises physicians to consider culture and susceptibility information and local epidemiology and susceptibility patterns when prescribing antibacterial therapy. The context of the statement in the "Information for Patients" section is very different from the other statements because it is information for physicians to convey to their patients. Patients should be advised not to skip doses of antibacterial therapy and to complete the full course of therapy, even if they start to feel better. Patients should also be advised that antibacterials do not treat viral infections.

(Comment 19) One comment asserted that standard statements about inappropriate use of antibacterial drugs do not merit the extraordinary prominence of appearing directly under the product name, thus giving the impression that these statements are the most important information about the product.

(Response) FDA believes it is important that the pressing public health problem of antibiotic resistance be highlighted in a prominent location. Furthermore, there is precedent for the appearance of a statement in this location. Oral contraceptives contain a statement under the product name indicating that they do not protect against sexually transmitted diseases. The antibiotic resistance statement, like the statement in oral contraceptive labeling, provides an important context for product use.

(Comment 20) Several comments stated that placement of a statement concerning antibiotic resistance under the product name would dilute the effectiveness of black boxed warnings, which are often placed there. One comment also claimed that the placement of a statement under the product name would conflict with FDA regulations at § 201.57(e) (21 CFR 201.57(e)) that reserve the area under the product name for boxed warnings, which, in turn, are reserved for critical safety information on hazards that may lead to death or serious injury.

(Response) FDA disagrees with the assertion that a statement under the