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Vincent R. Reinhart,

Secretary, Federal Open Market Committee.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 201

[Docket No. 00N-1463]

RIN 0910-AB78

Labeling Requirements for Systemic Antibacterial Drug Products Intended for Human Use

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending its regulations to require that the labeling for all systemic antibacterial drug products (i.e., antibiotics and their synthetic counterparts) intended for human use include certain statements about using antibiotics in a way that will reduce the development of drug-resistant bacterial strains. The final rule reflects a growing concern in FDA and the medical community that unnecessary use of systemic antibacterials has contributed to a dramatic increase in recent years in the prevalence of drug-resistant bacterial infections. The final rule is intended to encourage physicians to prescribe systemic antibacterial drugs only when clinically necessary. The final rule is also intended to encourage physicians to counsel their patients about the proper use of such drugs and the importance of taking them exactly as directed.

DATES: This rule is effective February 6, 2004.

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I. Background

In the **Federal Register** of September 19, 2000 (65 FR 56511), FDA proposed to amend its regulations to require that the labeling for all systemic antibacterial drug products (i.e., antibiotics and their synthetic counterparts) intended for human use include certain statements about using antibiotics in a way that will reduce the development of drug-resistant bacterial strains. The new labeling is intended to help educate physicians and the public about the resistance problem and to encourage physicians to prescribe systemic antibacterial drugs only when clinically necessary. FDA personnel involved in drafting the statements included practicing physicians who are in a position to evaluate the effect of the labeling on physicians. The statements were also reviewed by other practicing physicians in the agency.

Antibacterial resistance among disease-causing bacteria represents a serious and growing public health problem in the United States and worldwide. Many bacterial species, including the species that cause pneumonia and other respiratory tract infections, meningitis, and sexually transmitted diseases, are becoming increasingly resistant to the antibacterial drugs used to treat them. Several bacterial species have developed strains that are resistant to every approved antibiotic, thus severely limiting the therapeutic options available for adequate treatment. The incidence of resistance in both hospital- and community-acquired infections has increased dramatically in the past several years, making many common illnesses more difficult to treat than they were only 5 or 10 years ago.

According to the Centers for Disease Control and Prevention (CDC), half of the 100 million antibiotic prescriptions

a year written by office-based physicians in the United States are unnecessary because they are prescribed for the common cold and other viral infections, against which antibiotics are not effective (Ref. 1). Unnecessary use of antibiotics in hospitals is common as well. The more an antibiotic is used, the more likely it is that bacteria will develop resistance to it. Thus, using antibiotics when they are not necessary contributes to the increasing prevalence of antibacterial resistance without providing any patient benefit.

Educating physicians and the public about the resistance problem and discouraging unnecessary use of antibiotics are important steps to decrease the prevalence of antibacterial resistance and slow its future development and spread. FDA believes that professional labeling has an important role in that educational effort. Therefore, FDA is requiring that the labeling for systemic antibacterial drug products include certain statements about unnecessary use of antibiotics and the link between such use and the emergence of drug-resistant bacterial strains.

Recent reports of a reduction in antibiotic prescribing raise the hope that the trend in overuse of antibiotics can be reversed and provide additional support for the need to include information in labeling to ensure the continued safety and efficacy of antibiotics (Refs. 2 and 3). The studies reported were conducted in children seen in outpatient practice and have not been confirmed in either adults or hospitalized patients. Nevertheless, as the authors of the two studies and the editorial (Ref. 4) that accompanied them note, efforts to promote the appropriate use of antibiotics have likely contributed to a decrease in antibiotic prescribing. These authors observe that it is important to continue such efforts if these gains are to be maintained. The authors cite the ongoing role of the U.S. Public Health Service Action Plan (Ref. 5) to combat antimicrobial resistance. FDA is one of the three lead agencies for this plan. The plan indicates that educational efforts should be one of the highest priorities and placing information on the labeling of systemic antimicrobial products is specifically cited in the plan.

II. Highlights of the Final Rule

The final rule amends FDA regulations to require that all systemic antibacterial drug products (i.e., antibiotics and their synthetic counterparts) intended for human use contain additional labeling information

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

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

and pharmaceutical industry trade organizations, the American Medical Association (AMA), and the CDC in conjunction with FDA.

(Response) The agency agrees that labeling alone will not be sufficient to reduce or prevent antibiotic resistance. 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 which will ultimately shorten the development time of future antimicrobial products. The agency has an ongoing partnership with other 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 8) One comment urged FDA to focus on the effective implementation of existing guidelines, such as the CDC guidelines for the treatment of acute otitis media in children and the Sinus and Allergy Health Partnership guidelines for the treatment of acute bacterial sinusitis, as a means of addressing antibiotic resistance. The comment added that these guidelines are both comprehensive and able to be updated as new information becomes available, whereas labeling cannot be updated quickly.

(Response) Many responsible organizations issue guidelines for the treatment of various types of bacterial infections. FDA supports these efforts and has worked with many of the sponsoring organizations to develop guidelines for clinical studies and related matters. The agency disagrees that labeling cannot be updated as quickly as guidelines. Guidelines for the treatment of bacterial infections are not usually revised more often than every 2 years. If necessary, FDA's professional labeling can be revised in 2 years.

(Comment 9) Another comment stated that peer review of antimicrobial use and prescribing practices is preferred over static treatment guidelines and restrictions, given the complexity of the decisionmaking process in evaluating patients.

(Response) The labeling statements required by this final rule are not static treatment guidelines or restrictions. Furthermore, nothing in the final rule forecloses the use of peer review as a way of reducing antibiotic resistance. FDA recognizes that many different approaches can assist physicians in making good prescribing decisions.

(Comment 10) One comment asserted that resistant infections are most often acquired in hospitals and then spread to the community and, therefore, FDA should work with public health agencies and state boards of health to establish more effective hospital infection-control programs, rather than addressing the resistance problem through labeling.

(Response) FDA is working with the CDC and other public health agencies to establish more effective hospital infection-control programs and to develop means for educating physicians and communicating current information on the resistance problem. However, the agency believes that antibiotic resistance labeling is also needed as a part of a multifaceted attack on the resistance problem. FDA also notes that some resistant organisms, for example, penicillin-resistant *Streptococcus pneumoniae*, are acquired in the community, rather than in the hospital.

(Comment 11) One comment endorsed the development and implementation of a coordinated plan for monitoring antimicrobial resistance at the local level using standardized tests. This comment stated that the use of universally accepted standard tests is critical to the consistent and meaningful interpretation of surveillance data throughout the United States and that these standards need to be in place before collecting and collating surveillance data. Without such standards, collated surveillance data would be difficult to interpret and of very limited value.

(Response) FDA is working with the CDC and other agencies to develop tools and methods that will allow for a coordinated plan for monitoring antibiotic resistance. However, efforts to curb the development of antibiotic resistance should not be delayed pending the creation of such a monitoring plan.

(Comment 12) Another comment suggested requiring a special prescription blank for antimicrobials, formatted to include FDA criteria for prescribing antibiotics, and placing the responsibility on pharmacists to ensure that the criteria are met.

(Response) Such a restriction would be extraordinarily difficult to implement because of the large number of systemic

antibacterial products. The agency believes that measures less restrictive of medical practice are more reasonable at this time.

(Comment 13) One comment recommended that marketed antibiotics be evaluated and that older products with higher potential for inducing resistance (i.e., poor PKs and/or potency, single-step resistance development) be retired in favor of newer antibiotics with optimized PKs, potency, and multiple-step pathways. This comment contended that doctors need to be educated to prescribe improved antibiotics and asserted that the rule might hinder this goal.

(Response) FDA does not agree that newer antibiotics are necessarily preferable to older ones. While some newer antibiotics may require more than one pathway to develop resistance, newer antibiotics tend to be broad-spectrum, which, in itself, can increase the development of resistance.

(Comment 14) One comment stated that the antibiotic labeling proposal should be coordinated with other agency labeling initiatives.

(Response) Rulemaking requires an opportunity for the public to comment and thus have input into proposed agency actions. To make it easy for the public to comment on only those issues that are of interest, FDA generally pursues separate rulemakings for labeling proposals concerning different subjects. FDA has proposed to revise the content and format of labeling for prescription drugs (physician labeling rule) (65 FR 81082, December 22, 2000). The agency has received comments on the proposal and is in the process of finalizing it. Whether the requirements of the physician labeling rule will apply to a systemic antibacterial drug product will depend on the approval date of that product. For those systemic antibacterial drug products that must comply with the physician labeling rule by using the new format, the final physician labeling rule will explain where in the new format the statements required by § 201.24 should be placed and when implementation of the new format must be completed.

E. Scope and Implementation

(Comment 15) A number of comments addressed the scope of the proposal. One comment stated that resistance can also develop from using topical, veterinary, and antimycobacterial antibiotics, and that there should be education about all these sources. One comment stated that the proposed rule should also apply to prescription and over-the-counter (OTC) otic, ophthalmic, and topical agents. One

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

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

increase resistance if patients do not comply with the full course of therapy or otherwise alter the prescribed dosing regimen.

(Response) In response to the comments, the agency has decided not to use the words "appropriate" or "inappropriate" because it recognizes that determining appropriate use, and therefore what is not appropriate, involves many factors and requires the exercise of the physician's judgment in using available information to select an antibiotic for a particular patient in a particular context. Instead, FDA has revised the statement under the product name to directly link reducing antibiotic resistance with prescribing antibiotics only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria. Similarly, the statement in the "Precautions" section indicates that prescribing antibiotics in the absence of a proven or strongly suspected bacterial infection increases the risk of developing resistance.

(Comment 26) One comment offered the following examples of inappropriate use: (1) Using antibiotics for common respiratory viral infections, (2) using a broad-spectrum antibiotic when a narrower spectrum antibiotic would be more appropriate, (3) using an antibiotic with an excessively long half-life, and (4) using a less potent antibiotic when a more potent agent would be more appropriate. Another comment described inappropriate use as including the use of antibiotics to treat viral infections, failure to prescribe an adequate length of treatment, failure of patients to complete the entire course of treatment, and skipping doses. This comment stated that it is important for physicians and the public to understand the basic value of antibiotics and went on to say that only inappropriate usage should be highlighted as requiring further education and restraint.

(Response) As discussed in the response to comment 25, the agency has decided not to use the words "appropriate" or "inappropriate" in the labeling statements required by this rule. The agency agrees, however, that examples of inappropriate use may include using antibiotics for viral infections, failure to prescribe an adequate length of treatment, failure of patients to complete the entire course of treatment, skipping doses, and using a broad-spectrum antibiotic when a narrower spectrum antibiotic would be more appropriate. The agency does not agree that it is never appropriate to use an antibiotic with a very long half-life. Half-life is a factor to be considered along with other many other specific factors involved in patient management,

but it is not appropriate to make generalizations about it in the context of this rule. Furthermore, focusing on the potency of an antibiotic is not a helpful approach because there is no standard definition of the potency of an antibiotic.

(Comment 27) The agency received the following five suggestions for wording to appear in place of that proposed to appear under the product name. Suggestions 1 through 4 were also proposed for the "Precautions" section:

1. "Inappropriate use of antibiotic products may increase the prevalence of drug resistant microorganisms, leading to a potential decrease in the general overall effectiveness of antimicrobial agents."

2. "Appropriate use of antimicrobial agents may help decrease the prevalence of drug resistant microorganisms, resulting in the continued effectiveness of this product and related agents. This product should be used only to treat infections that are strongly suspected or proven to be caused by susceptible microorganisms."

3. "Inappropriate use of an antibiotic may increase the prevalence of drug-resistant microorganisms and may decrease the future effectiveness of the antibiotic and related antimicrobial agents. It is not appropriate to extrapolate the benefit/risk profile established in patients with documented bacterial infections to other patients (e.g., patients with viral infections). This antibiotic does not treat viral infections."

4. "Appropriate antibiotic use requires the selection of an antibiotic, for a known or suspected bacterial infection, that optimizes clinical therapeutic effect by maximizing bacteriological eradication and minimizing the development of resistance and drug-related toxicity. In order to eradicate the bacteria and minimize the development of bacterial resistance, it is important to administer the appropriate antibiotic at the right dose and for the right duration. See Dosage and Administration Section."

5. "Inappropriate use of antibacterial agents, including (insert name of antibacterial drug product) may increase the prevalence of drug resistant bacteria and may decrease the effectiveness of antibacterial agents, including (insert name of antibacterial drug product). (Insert name of antibacterial drug product) should be used only to treat infections that are proven or suspected to be caused by indicated bacteria."

Suggestion 5 eliminates from the proposed phrase "strongly suspected" the word "strongly," contending that it adds nothing.

The agency also received a suggestion intended only for the "Precautions" section:

"Inappropriate use of antibacterial agents, including (insert name of antibacterial drug product) may increase the prevalence of drug resistant bacteria and may decrease the effectiveness of antibacterial agents, including the drug product. Antibacterial agents, including the drug product, should be used to treat infections that are proven or suspected to be caused by indicated bacteria. The antibacterial agent chosen to treat a documented or presumptive bacterial infection should be targeted to the most likely bacterial pathogen(s) and should have the narrowest spectrum possible to cover the likely pathogen(s)."

(Response) All of the previous wording suggestions are phrased in terms of either inappropriate or appropriate use. The agency has been persuaded by the comments that using the words "inappropriate" or "appropriate" is confusing and unhelpful; therefore, the final rule does not use these terms. Because FDA has decided not to use the words "inappropriate" or "appropriate," the agency declines to adopt any of the wordings suggested in the comments. The agency disagrees with the opinion that there is no difference between "suspected" and "strongly suspected." Since many infections could theoretically be either viral or bacterial, the direction to use antibiotics for suspected bacterial infections could be interpreted as approving of antibiotic use whenever there is a possibility of a bacterial infection. Therefore, the final rule retains the word "strongly."

H. Culture and Susceptibility Tests

Proposed § 201.24(b) would have required the following statement in the "Clinical Pharmacology" section: "Appropriate use of (insert name of antibacterial drug product) includes, where applicable, identification of the causative microorganism and determination of its susceptibility profile."

(Comment 28) Many comments objected to this statement, asserting that it is not always possible or advisable to do cultures. Comments stated that for the majority of infections, including respiratory tract infections, obtaining a specimen for a culture is not possible. One comment objected that diagnostic tests that immediately distinguish viral and bacterial infections are not available.

(Response) The agency recognizes that it is not possible to obtain specimens for cultures for many common community-

acquired infections, including many respiratory tract infections and *otitis media*. FDA also agrees that there are no diagnostic tests that can immediately determine whether an infection is bacterial or viral. The revised statement for the "Indications and Usage" section recognizes these realities by advising that culture and susceptibility information should be considered in selecting or modifying antibacterial therapy when it is available.

(Comment 29) Many comments stated that the majority of infections, especially those acquired in the community rather than in the hospital, are and should be treated empirically without waiting for identification of the causative microorganism. One comment asserted that antibiotics must be initiated empirically for a febrile neutropenic patient or a patient with pneumonia in an intensive care unit (ICU). Another comment stated that the American Thoracic Society Guideline for Pneumonia recommends empirical treatment of pneumonia and concludes that Gram stains of sputum, cultures, and susceptibility testing are not cost-effective, particularly for outpatient infection. One comment stated that to delay the start of treatment waiting for culture results would be unethical as well as impractical. Another comment maintained that when patients are at risk of serious complications from infection, they must be treated empirically, and broad-spectrum therapy may be used to avoid treatment failure. Another comment stated that the agency has not considered outcome data concerning the benefits of empiric treatment on mortality and morbidity. One comment stated that doctors should decide whether to change antibiotic therapy based on the clinical situation, not only on in vitro susceptibility data. Another comment stated that there are not many efforts to gather information on treatment outcomes in ambulatory settings. One comment asked what the agency meant by the phrase "where applicable" in the statement: "Appropriate use of (*insert name of antibacterial drug product*) includes, where applicable, identification of the causative microorganism and determination of its susceptibility profile."

(Response) FDA agrees that antibiotic therapy must often be initiated empirically, including for patients with febrile neutropenia or ICU patients with pneumonia, and that it may be unethical to delay the initiation of therapy. FDA recognizes that in many situations physicians must make difficult choices about the need for empiric therapy and broad-spectrum agent use. Most clinical

guidelines concerning the management of such situations also recommend taking measures to alter treatment to more targeted antimicrobial coverage, such as through the use of bacterial cultures, whenever possible.

The agency did not intend to call for physicians to always refrain from initiating antibiotic therapy until the causative microorganism has been identified. The statement proposed for the "Indications and Usage" section recommended that initial selection of an antibiotic be guided by local epidemiology and susceptibility patterns, thus clearly contemplating that antibiotic therapy would be initiated before the results of culturing had been obtained. In addition, the modifier "where applicable" was intended to indicate that it is not always possible to do culture and susceptibility testing.

In response to comments, the agency has revised the statements about the role of culture and susceptibility tests and the use of local epidemiology and susceptibility patterns to make clear that FDA is not advising physicians that they should never prescribe antibiotics without first obtaining culture and susceptibility results or without referring to local epidemiology and susceptibility patterns. The agency has decided that the statement about culture and susceptibility information is more appropriate for the "Indications and Usage" section than for the "Clinical Pharmacology" section. The statement suggests that after initiating antibiotic therapy empirically, physicians should consider modifying therapy if susceptibility information becomes available and indicates that the microorganisms causing the infection are different from those initially suspected. FDA recognizes, however, that the physician must also weigh the clinical situation.

(Comment 30) One comment asserted that there is no scientific consensus on the need to use narrow-spectrum antibiotics targeted at organisms that have been identified through cultures.

(Response) FDA believes that using narrower spectrum, more targeted therapy, to treat a known organism can reduce the development of resistance. Narrower spectrum antimicrobials may have less impact on the normal organisms that colonize the body. Normal flora may protect the body from becoming colonized with other, more pathogenic bacteria. Also, normal flora exposed to an antimicrobial may become resistant to that antimicrobial and pass resistance genes on to more pathogenic bacteria. Therefore, prescribing narrower spectrum drugs may limit the spread of resistance while

still treating the pathogenic organisms causing the disease. This subject was discussed by presenters and panel members at the January 8, 2003, Anti-Infective Drugs Advisory Committee meeting. However, the labeling statements in the final rule do not dictate the use of narrow-spectrum antibiotics.

(Comment 31) Comments maintained that there are not enough laboratories to perform susceptibility testing for all of the antibiotics prescribed and that, in many parts of the country, physicians do not have access to susceptibility testing. One comment stated that few clinics have access to local microbiology labs; that the majority of microbiological diagnostic testing is done in central locations by a few laboratories, and that many hospitals do not have microbiology laboratories. This comment noted that the Infectious Disease Society of America has recently issued a position paper on the lack of access to microbiology laboratories and the threat that this lack of facilities poses to the public health. Two comments stated that the regulations of the Clinical Laboratory Improvement Act provide that Gram stains should be performed and interpreted by qualified lab technicians, not doctors.

One comment stated that the infrastructure required to support diagnostic testing in primary care settings is not in place and that diagnostic testing is not likely to be funded unless there are data to support the cost-effectiveness of doing culture and susceptibility testing rather than using broad-spectrum antibiotics. This comment also stated that the pharmaceutical industry should not have to fund such testing. Another comment stated that managed care and third-party payers have not funded the infrastructure required for diagnostic testing in primary care settings.

(Response) FDA agrees that some physicians lack access to facilities that perform susceptibility testing. The agency also agrees that it is not the responsibility of the pharmaceutical industry to make such testing available. The final rule's statement in the "Indications and Usage" section takes into account that culture and susceptibility information may not always be available.

I. Local Epidemiology and Susceptibility Patterns

Proposed § 201.24(c) would have required the following statement in the "Indications and Usage" section:

Local epidemiology and susceptibility patterns of the listed microorganisms should direct initial selection of (*insert name of*

antibacterial drug product) for the treatment of the following indications. Because of changing susceptibility patterns, definitive therapy should be guided by the results of susceptibility testing of the isolated pathogens.

(Comment 32) One comment stated that the direction to use local epidemiology and susceptibility patterns is not practical because this information is not available to doctors. Another comment stated that lack of susceptibility data on a particular product in a particular geographic region should not contraindicate use of the drug. Several comments stated that various practice guidelines do not recommend the use of surveillance data to guide antibiotic therapy. Another comment stated that there are different datasets of susceptibility data and asked which set should be used. This comment also stated that susceptibility patterns can change rapidly, making data obsolete.

(Response) FDA recognizes that surveillance data on microbial sensitivities may not be available in some settings and are not helpful in other situations. However, in many circumstances, the data provide a source of information that may assist the prescriber in the selection of empiric therapy. FDA suggests that physicians obtain epidemiology and susceptibility data from local hospitals or State health departments. Physicians who have access to such sources of information and make it a practice to update their information periodically can remain current on susceptibility patterns in their areas.

(Comment 33) One comment contained the following detailed objections to the use of susceptibility data:

- MIC data from in vitro testing are unproven as predictors of clinical outcome in many diseases.
- Susceptibility data obtained from surveillance studies have limitations for prospective therapeutic decisions. These limitations include the fact that large national and international surveillance studies obtain data from hospitalized patients who are more likely to have resistant isolates. These data are unlikely to be linked to clinical data so that the relevance of the MIC values generated is limited.
- Local surveillance data can be biased because of small sample sizes. The data that are likely to be available to physicians in the community come from clinical trials that exclude patients who would be at risk for resistant isolates.
- Laboratory methodology and expertise can influence susceptibility

testing, e.g., E tests often err for drugs that are highly dependent on pH for activity, which is a particularly important problem for macrolides such as erythromycin and clarithromycin.

- Clinical outcome data are not the basis for current National Committee for Clinical Laboratory Standards (NCCLS) and FDA breakpoints for most drugs used for outpatient respiratory tract infections. The NCCLS changed the breakpoints for some beta-lactam antibacterials and that has altered the susceptibility rates.

(Response) The agency agrees that surveillance data has limitations; however, data with limitations may still be useful. Accordingly, the revised statement in the "Indications and Usage" section states that local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy when culture and susceptibility information are not available.

(Comment 34) One comment contended that recommending the use of local epidemiology and susceptibility patterns will lead to the use of newer, possibly broad-spectrum agents that have lower rates of in vitro resistance, although older agents are still appropriate choices. This comment also stated that other factors may be useful in selecting antibiotic therapy. For example, molecular resistance mechanisms for particular bacteria may be useful to predict clinical efficacy, and the location of infection predicts response to therapy in some diseases.

(Response) FDA agrees that it is not reasonable to focus solely on epidemiology and susceptibility patterns as the decisive factor in selecting an antibiotic. Most clinicians use this information as one of many factors considered in deciding which drug to use.

(Comment 35) Two comments suggested alternative wording for the statement to appear in the "Clinical Pharmacology" section as follows:

1. "Appropriate use of this product may include, where applicable and practical, identification of the causative microorganism and the determination of its susceptibility profile."

2. "Appropriate use of antibacterial agents includes, where applicable, identification of the causative bacteria and determination of its susceptibility profile. The pharmacokinetic and pharmacodynamic profile of the agent and the location of the infection should also be considered when selecting an appropriate antibiotic for treatment of a documented or presumptive infection."

(Response) The previous two wording suggestions are modified versions of the

statement that was proposed for the "Clinical Pharmacology" section. The final rule does not require a statement in the "Clinical Pharmacology" section because the agency has decided that advice about obtaining cultures belongs in the "Indications and Usage" section rather than the "Clinical Pharmacology" section. Therefore, FDA declines to adopt either of these suggestions.

(Comment 36) The agency received three suggestions for wording to appear in the "Indications and Usage" section as follows:

1. "Appropriate culture and susceptibility tests should be performed before treatment in order to isolate and identify organisms causing infection and to determine their susceptibility to (name of drug). Therapy with (name of drug) may be initiated before results of these tests are known; once results become available, appropriate therapy should be continued."

2. "Appropriate specimens for bacteriological examination should be obtained, when indicated and feasible, in order to isolate and identify causative organisms and to determine their susceptibility to [name of product]. Therapy may be instituted while awaiting the results of these studies. Once these results become available, antimicrobial therapy should be adjusted accordingly."

3. "The efficacy of this drug has been demonstrated when it is used as directed for the indications and susceptible pathogens listed below. Use of this drug in other regimens or for other indications or pathogens may be ineffective. Inappropriate use of this or other antibacterials may increase the prevalence of drug resistant microorganisms. The prescription of antimicrobial therapy should be guided, when possible, by the results of local or regional susceptibility testing of causative pathogens typically isolated during the infection. When microbiological data are not available for an individual patient, the decision to prescribe an antibiotic should be based on the clinician's assessment of the most likely etiology and optimal therapy based on the available clinical, pharmacodynamic, and in vitro information provided from clinical trials and post-marketing experience with antimicrobial agents."

(Response) The agency declines to adopt the specific wording in any of these suggestions. However, the revised statement for the "Indications and Usage" section incorporates many ideas from these suggestions. The idea that therapy may be initiated before obtaining culture results is captured by the statement that antibiotics may be

used to treat infections that are strongly suspected to be bacterial. The statement that culture and susceptibility information should be considered when available captures the idea expressed by such phrases as "where applicable and practical" and "when indicated and feasible." FDA's statement also includes the idea that physicians may wish to modify antibiotic therapy after obtaining the results of susceptibility testing.

J. Practice of Medicine

(Comment 37) Many comments asserted that the proposal is outside the scope of labeling, the purpose of which is to provide the information necessary for the safe and effective use of drugs, not to tell physicians how to practice medicine. One such comment maintained that product labeling should not dictate medical practice, which requires individualized clinical assessment of the patient and the circumstances under which the patient is being treated, and that FDA's role does not include teaching medicine. Another comment asserted that the proposal interferes with the practice of medicine since the choice of antibiotic should be made by the physician after weighing the overall benefits and risks to the patient. Another comment stated that labeling should not impose a specific standard of care or practice that must be followed. Another comment maintained that there is no statutory basis for FDA to regulate physician conduct or train physicians and that the clinical knowledge gained from years of medical training and experience cannot be completely provided for in labeling.

Several comments expressed concern that the proposed labeling statements would result in legal liability for physicians because in many cases they would not be able to follow the standard of practice required by the labeling, that is, obtaining cultures to identify microorganisms and determine their susceptibility profiles.

(Response) The agency disagrees with comments maintaining that the proposed rule is outside the scope of labeling. As FDA has long recognized, its role is neither to regulate physician conduct, nor to train physicians. As FDA wrote in 1972:

Throughout the debate leading to enactment (of the 1938 Act and the drug amendments of 1962), there were repeated statements that Congress did not intend the Food and Drug Administration to interfere with medical practice and referenced to the understanding that the bill did not purport to regulate the practice of medicine as between the physician and the patient . . . 37 Fed. Reg. at 16503.

FDA's 1972 notice continues:

{A}lthough it is clear that Congress did not intend the Food and Drug Administration to regulate or interfere with the practice of medicine, it is equally clear that it did intend that the Food and Drug Administration determine those drugs for which there exists substantial evidence of safety and effectiveness and thus will be available for prescribing by the medical profession, and additionally, what information about the drugs constitutes truthful, accurate, and full disclosure to permit safe and effective prescription by the physician. As the law now stands, therefore, the Food and Drug Administration is charged with the responsibility for judging the safety and effectiveness of drugs and the truthfulness of their labeling. The physician is then responsible for making the final judgment as to which, if any, of the available drugs his patient will receive in the light of the information contained in their labeling and other adequate scientific data available to him.

Physicians have been concerned that the failure to follow the labeling of a drug may render them unduly liable for malpractice.

Although labeling, along with medical articles, tests, and expert opinion, may constitute evidence of the proper practice of medicine, it is not controlling on this issue. The labeling is not intended either to preclude the physician from using his best judgment in the interest of the patient, or to impose liability if he does not follow the package insert. A physician should recognize, however, that the package insert represents a summary of the important information on the conditions under which the drug has been shown to be safe and effective by adequate scientific data submitted to the Food and Drug Administration.

Given this framework, it is appropriate to include in labeling information necessary for the safe and effective use of the drug, including information about the context of product use. For example, labeling for anesthetic agents often includes very specific recommendations about the conditions under which the products should be used and the training of the personnel who administer them. Furthermore, many approved antibiotics already recommend that appropriate culture and susceptibility tests be performed.

FDA has adopted revised statements to address concerns expressed in the comments that the proposed rule categorically dictated medical practice and held up a standard that physicians would be unable to meet. The revised statements take into account that culture and susceptibility information are not always available. In addition, rather than stating that local epidemiology and susceptibility patterns should help direct initial selection of antibiotic therapy, the final rule provides that information from these sources may contribute to the selection of therapy.

With these changes, the agency believes that the statements required by the final rule cannot be interpreted as overly directive and thus do not interfere with the practice of medicine. The final rule is not intended to establish a standard of care. The rule is designed to provide information and context for health care providers to consider in prescribing certain medications.

K. Information for Patients

The proposed rule provided that the following statement appear in the "Precautions" section under the "Information for patients" subsection:

Patients should be counseled that (*insert name of antibacterial drug product*) should only be used to treat bacterial infections. It does not treat viral infections (e.g., the common cold).

Patients should also be told that the medication should be taken exactly as directed. Skipping doses and 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 that will not be treatable by (*insert name of antibacterial drug product*) in the future.

(Comment 38) The comments were generally supportive of the proposal to educate patients. However, one comment stated that FDA's attempt to educate the public through labeling is misguided. The comment pointed to a study¹ evaluating a medication guide that found that less than 50 percent of the patients who received the guide read it; that of the patients who read the guide, only 50 percent could recall at least one issue discussed in it; and that only 20 percent of the patients who knew the contents of the guide said they had taken some action based on it. This comment stated that if the agency proceeded with the proposal to include a statement for patients, the statement should be: "Patients should be counseled to take all medicinal products exactly as directed."

(Response) The agency does not believe the medication guide study is relevant to the labeling proposal concerning antibiotic resistance because the agency has not proposed a medication guide or anything else for patients to read. The "Information for patients" subsection contains information that would be communicated to the patient by the prescriber. The agency disagrees with the suggestion that patient information be limited to advising patients to take all medications exactly as directed because that advice would not explain

¹ Chianese, C. P., "An Overview of an Initial Experience With a Medication Guide," *Drug Information Journal*, vol. 34, pp. 855-859, 2000.

the specific consequences of failure to take antibiotics as directed.

(Comment 39) One comment asserted that, as written, the statement could suggest that patients are qualified and capable of diagnosing their own infections. Another comment stated that patient information should primarily reinforce the prescribed dosing because patients should not be expected to know how to distinguish between viral and bacterial infections. The comment also asserted that patients should be educated that at least one office visit is necessary to decide whether an antibiotic should be prescribed. Another comment stated that pharmacists should give patients the entire package insert rather than a summary, because patient demand for antibiotics often leads to unnecessary prescribing.

(Response) FDA does not agree that its proposed language suggests that patients are capable of diagnosing their own infections or are able to tell the difference between a viral and a bacterial infection. Generally, FDA expects that information concerning the use of antibiotics would be communicated to the patient in the doctor's office after the patient had already decided to seek medical care. However, because antibiotics are prescribed in hospitals as well as on an outpatient basis, FDA declines to adopt the suggestion that patients be told that at least one office visit is necessary. It is not clear how giving the package insert to patients who are prescribed antibiotics would reduce patient demand for antibiotics. In any event, FDA usually requires patient package inserts only when there is a need to communicate detailed risk information about a drug product or instructions for using the product. Neither of these circumstances apply to systemic antibacterial drug products.

(Comment 40) One comment stated that the patient information statement should not apply to any antibiotic administered solely via intravenous or intramuscular routes because patients do not self-administer by these routes.

(Response) FDA disagrees with the notion that patients never self-administer antibiotics by intravenous or intramuscular routes. Patients who are started on intravenous antibiotics in the hospital sometimes continue to use injectable antibiotics on an outpatient basis. Therefore, the patient information section must be included in the labeling of systemic antibacterials administered intravenously or intramuscularly.

(Comment 41) The agency received many specific suggestions for revisions to the proposed patient statement. One comment proposed the following

language: "Patients should be counseled about the differences between viral and bacterial infections." One comment suggested adding the phrase "the oral antibiotic" before the name of the product in the first sentence. Another suggestion was to add the words "despite feeling better or 'totally' well" after the phrase "Skipping doses and not completing the full course of therapy." Another comment suggested using the phrase "likelihood of selecting bacteria" rather than the phrase "likelihood that bacterial will develop."

Two comments suggested adding either "antibacterial drugs, including" or "antibacterial agents including" before the product name in the first sentence. One comment suggested replacing the specific product name in the last sentence with the phrase "antibacterial drugs," while another comment proposed to add "or other antibacterials" after the product name in the last sentence. In the sentence "Skipping doses and 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 that will not be treatable by (*insert name of antibacterial drug product*) in the future," one comment proposed to replace the first "will" with "may," while another comment suggested replacing both instances of the word "will" with the word "may."

(Response) In the final rule, FDA has adopted a number of the suggestions made in the comments. FDA has adopted the suggestion to precede the name of the product in the first sentence with the phrase "antibacterial drugs including" because the information applies to all antibacterial drugs. The agency also agrees with the idea of adding the phrase "or other antibacterials" to the last sentence, but has altered the wording slightly to state "or other antibacterial drugs." FDA agrees with the concept that patients should be told to continue therapy even after they feel better and has included the phrase "Patients should be told that although it is common to feel better early in the course of therapy * * *" in the statement.

FDA declines to adopt other suggestions. The agency believes that the suggestion that patients be counseled about the differences between bacterial and viral infections is not as direct as and, therefore, not preferable to FDA's revised language. FDA does not agree that the phrase "the oral antibiotic" should be added because the implication of this suggestion is that patients are never responsible for using injectable antibiotics. As discussed

previously, there are circumstances where injectable antibiotics are self-administered. The agency rejects the suggestion to use the phrase "likelihood of selecting bacteria" because most lay people are not familiar with the concept of bacterial selection. The agency declines to adopt the suggestions to use "may" rather than "will" in the phrases "will develop" and "will not be treatable." The concept of possibility rather than certainty is already expressed by the words "may" and "likelihood" earlier in the sentence.

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 Impacts

FDA has examined the impacts of the final rule under Executive Order 12866, 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 alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). Under the Regulatory Flexibility Act, if a rule has a significant economic impact on a substantial number of small entities, an agency must consider alternatives that would minimize the economic impact of the rule on small entities. Section 202(a) of the Unfunded Mandates Reform Act of 1995 requires that agencies prepare a written statement of anticipated costs and benefits before proposing any rule that may result in an expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of \$100 million in any one year (adjusted annually for inflation).

The agency believes that the final rule is consistent with the regulatory philosophy and principles identified in Executive Order 12866 and in these two statutes. The final rule will amend the content of the professional labeling for human prescription antibacterial drugs. Based on the analysis, summarized in table 1 of this document, FDA projects the annualized costs to comply with the final rule to be less than \$600,000. The agency finds that if the revised labeling reduces direct and indirect costs attributable to resistant bacteria by 1

percent, the annual benefit will exceed \$10 million. Thus, while it has been determined that the final rule is significant under the Executive order, the final rule will not be economically significant as defined by the Executive order, because the annual impacts on the economy are substantially below

\$100 million. With respect to the Regulatory Flexibility Act, the agency certifies that this final rule will not have a significant effect on a substantial number of small entities. The effect of small entities is discussed in more detail in section V.D of this document. The Unfunded Mandates Reform Act

does not require FDA to prepare a statement of costs and benefits for the final rule because the rule will not result in any 1-year expenditure that would exceed \$100 million adjusted for inflation. The current inflation-adjusted statutory threshold is about \$110 million.

TABLE 1.—SUMMARY OF QUANTIFIABLE BENEFITS AND COSTS (\$MILLION)

Benefits and Costs	One-Time	Annual	Total
Benefits¹			
Avoided cost of hospital infections		3.8	3.8
Indirect cost of longer hospital stays		0.4	0.4
Indirect costs of mortality (discounted at 3% and 7%)		6.6–11.8	6.6–11.8
Total Benefits		10.8–16.0	10.8–16.0
Costs²			
One-time labeling revision	2.9		0.42
Annual incremental printing cost		0.02	0.02
Annual Physicians Desk Reference (PDR)		0.123	0.123
Total Costs	2.9	0.146	0.568

¹ Assumes medical, productivity, and mortality costs now attributable to antibacterial resistance are reduced by 1 percent.

² May not sum to total because of rounding.

A. Objective of the Final Rule

Drug-resistant bacteria pose a public health risk by reducing the effectiveness of prescription antibacterial drug products. Some disease-producing bacteria can adapt and become resistant to newly developed drugs within a couple of years. For example, a report of infections resistant to linezolid, the first drug in a new class of antibiotics, was published just 1 year after its approval (Ref. 6). To stress the need for continued vigilance against the emergence of resistant bacteria, the final rule requires that labeling of systemic antibacterial drug products include statements that encourage the use of antibiotics in a way that reduces the risk of developing drug-resistant bacteria. The final rule requires that labeling for affected prescription drug products comply with the requirements by February 6, 2004.

B. Costs of Regulation

The agency received several comments about the costs of the proposed rule. One comment asked whether the economic analysis in the proposed rule included the cost of initial and followup doctor visits or the cost of culture and sensitivity tests. Because patients normally see a health care provider to obtain a prescription for an antibacterial drug, the agency's initial analysis of impacts did not include costs for health care visits.

The agency also did not estimate the number or cost of laboratory tests that might have been ordered because of the proposed labeling change. Many doctors

and hospitals currently order susceptibility tests, especially when there is a high incidence of resistant bacterial infections locally. In any event, in response to comments, the agency has revised the wording of the proposed statement that suggested a general need for susceptibility testing. Instead, the final rule adds statements to antibacterial labeling that remind health care providers to consider laboratory results, if available, when selecting drug therapy. Because the final rule does not require additional laboratory tests or visits to health care providers, this analysis of impacts does not include these patient health care costs as regulatory costs.

Some comments questioned the cost-effectiveness of susceptibility testing. The agency did not evaluate the cost-effectiveness of laboratory tests. As stated elsewhere in the preamble, the agency has modified the language about susceptibility tests to clarify that initial drug therapy should be modified if available test results suggest the infection is caused by different microorganisms than initially suspected, not by testing each patient.

One comment stated that waiting to initiate drug therapy would lead to additional health care, morbidity, and mortality costs. While the agency agrees that any delay in starting therapy can increase the direct and indirect costs of infection, the final rule does not suggest that health care providers postpone treatment once they strongly suspect that an infection is caused by a bacteria.

The agency agrees that costs increase when resistant bacteria are not initially identified as the cause of an infection. In one study on bloodstream infections, the length of hospital stay increased by 6.4 days and mortality increased from 11.9 percent to 29.9 percent with inadequate treatment (defined as either giving an incorrect drug for an infection-causing pathogen or giving the correct drug for an infection-causing pathogen that is resistant to the drug) (Ref. 7). The objective of the final rule is to reduce the prevalence of and costs associated with resistant bacteria and their associated costs. A more detailed discussion of avoided costs follows in section V.C of this document.

1. Affected Products

The final rule will affect all systemic antibacterial drug products except those primarily indicated to treat a mycobacterial infection. Antifungal, antiviral, antiparasitic, and topical antibacterial products will not be subject to the labeling requirements of the final rule. FDA estimates that manufacturers will be required to modify labeling of 669 antibacterial drug products.²

² Derived from FDA's *Approved Drug Products With Therapeutic Equivalence Evaluations*, 2002, and *2001 Drug Information*, American Hospital Formulary Service (AHFS). Products counted and active ingredients matching the AHFS lists of antibacterial agents, and a distinct manufacturer, active ingredient, or dosage form. Topical dosage forms were excluded. Products with different

Continued

2. Professional Labeling Design Costs

For a major revision in the content of professional labeling, FDA had estimated in its preliminary analysis that, on average, prescription drug manufacturers would incur costs of about \$2,600 per product, including inventory loss, because the 12-month implementation period is shorter than the average useful life of pharmaceutical labeling. To derive this estimate, labeling costs for four categories of pharmaceutical manufacturers were weighted by their market share of all

pharmaceutical products. Comments from a large pharmaceutical manufacturer, however, stated that labeling redesign costs to industry are more than three times FDA's estimate. In response, the agency has recalculated the market shares of the affected antibacterial products based on its current drug approval data (table 2). Adjusting for both inflation and market shares, FDA now estimates that manufacturers of antibacterial drugs will incur, on average, per product costs of approximately \$4,380, including \$1,040 in inventory loss. The weighted

average cost to revise drug labeling is based on input from industry consultants on the time and materials required to modify the package insert accompanying pharmaceutical products. (Table 2a shows a breakdown, by firm size, of the labor and material costs used to derive the weighted average cost of \$4,380.) While some firms may incur per product costs higher than the average estimate, the agency believes that the revised per product cost represents a reasonable estimate of industrywide costs.

TABLE 2.—MARKET SHARE OF AFFECTED ANTIBACTERIAL DRUG PRODUCTS BY CATEGORY OF FIRM

Category of Firm	Number of Firms	Number of Products	Market Share ¹
Innovator ²			
Small ³	10	18	2.69%
Medium	3	27	4.04%
Large	45	501	74.89%
Generic ⁴	43	123	18.39%
Totals	101	669	100.00%

¹ May not sum to total because of rounding.

² Includes firms manufacturing both innovator and generic products.

³ Includes 7 private firms without size data.

⁴ Includes firms manufacturing only generic products and 26 private firms without size data.

TABLE 2A.—LABELING REVISION COSTS BY FIRM SIZE

Item	Generic Drug Manufacturers	Innovator Drug Manufacturers		
		Small	Medium	Large
Labor Cost	\$830	\$830	\$1,242	\$1,812
Material Cost	\$740	\$740	\$2,230	\$3,400
Total Cost to Revise Labeling	\$1,570	\$1,570	\$3,472	\$5,212

3. Incremental Printing Costs for Professional Labeling

No comments were received on FDA's estimate of incremental printing costs for longer labeling. Therefore, FDA maintains its estimate that an average of 100,000 package inserts are printed annually for each antibacterial drug product marketed in the United States.³ Compared to the proposed rule, the final rule requires fewer statements in the labeling, thus reducing the costs to print longer labeling. Adding new information on prudent use of antibacterial drug products to professional labeling will increase the

size of current package inserts by an estimated 3.3 percent or 3.3 square inches (in²) for the average insert. Although few package inserts will change size, if all manufacturers had to increase the length of the package insert to accommodate the new statements, they would incur additional printing costs of about \$37 per affected product.⁴ If all affected products had longer labeling, printing costs for the industry would increase by less than \$25,000 annually.

4. PDR Costs

No comments were received on the impact of the rule on PDR costs for

manufacturers. According to its publisher, a page in the print version of the PDR costs an average of \$9,500 in 2001.⁵ Furthermore, according to the publisher of the electronic versions of the PDR, each full package insert published in the print version is also included in the Internet and CD-ROM versions of the PDR at no additional cost to the drug manufacturer. A search of the Internet version of the PDR showed that as many as 160 antibacterial drug products will have slightly longer descriptions in the PDR.⁶ The additional

therapeutic equivalence codes for the same manufacturer were counted separately.

³ In 1996, there were approximately 133 million prescriptions for antibacterial drugs written by physicians in office and hospital settings (Government Accounting Office, 1999). An estimated 45.3 million inserts were printed to accompany these drugs. (45.3 million = (106 retail prescriptions/3 prescriptions per container) + (19 million hospital emergency prescriptions/2 prescriptions per container) + (8 million hospital outpatient prescriptions/500 units per container/ (28 units per prescription))). An average of 56,767

inserts therefore accompanied each product (45.3 million ÷ 798 products). Also, we assume that 40,000 additional inserts per product are distributed annually by sales representatives as promotional material.

⁴ Although the length of an average package insert will only increase by 3.3 in², we rounded to 4 in² to calculate costs. The 1997 estimated incremental printing cost of \$ 0.0086 per 100 in² was adjusted for inflation by the producer price index for commercial printing (i.e., a 6 percent increase in costs between 1997 and April 2001). \$36.53 =

100,000 inserts per product x 1.06 x \$0.000086 per in² x 4 in².

⁵ \$9,500 is the estimated average industry cost. Per page charges to an individual firm will decrease as more PDR pages are purchased. The maximum per page charge listed on Medical Economics' 2001 rate card is \$19,035 (i.e., less than eight pages purchased for the year).

⁶ A search of the Internet version of the PDR by affected drug category and by indication found only 156 affected products. According to Micromedex (<http://www.micromedex.com>), all fully described

language will add less than one-tenth of a page to an average PDR listing and cost about \$842 more per product.⁷ The annual costs of printing the larger labels

in the PDR, therefore, will increase by \$0.13 million.

Over 10 years, the agency estimates that the annualized compliance costs of

the final rule will be approximately \$580,000. These costs are summarized in table 3.

TABLE 3.—COSTS TO REVISE PROFESSIONAL LABELING AND INCREMENTAL PRINTING COSTS

	One-Time Labeling Revision Costs	Annual Incremental Printing Costs	Annual PDR Costs
Per product cost ¹	\$4,379	\$37	\$842
Number of affected products	669	669	160
Total	\$2,929,228	\$24,439	\$134,720
Total annualized costs ²	\$417,056	\$24,439	\$134,720

¹ Rounding may affect totals.

² One-time costs are annualized over 10 years at 7 percent.

C. Benefits

Bacterial resistance to antibacterial drugs directly affects health care costs by requiring the use of newer and more expensive drugs and by requiring longer treatment and hospitalization periods for patients infected by resistant bacteria. The societal costs of the infections from these resistant bacteria include both the direct costs for additional drugs and medical care and the indirect costs of lost productivity for patients with extended illness and increased mortality. The agency did not receive any direct comments on the benefits estimate in the proposed rule. However, during the review of the proposed rule, the Office of Management and Budget (OMB) requested that the agency estimate mortality attributable to resistant bacteria for the final rule. Thus, the final analysis of impacts also includes an estimate of the number of lifeyears saved.

1. Direct Costs of Resistant Infections

Most studies on the cost of hospital infections in the United States have not separated infections caused by resistant bacteria from those caused by susceptible bacteria. Researchers from the CDC, examining summary reports of outbreak investigations for 1971 through 1980, as well as published and unpublished reports of infections caused by bacteria with known antibacterial resistance, found that infections from resistant bacteria were typically associated with substantially longer hospital stays. The examined studies, however, had too few subjects to allow statistical analysis (Ref. 8).

Two recent studies on the effects of methicillin-resistant *Staphylococcus aureus* (MRSA) reported significantly different lengths of stay for patients infected with resistant bacteria compared to controls. The studies

included only patients with similar underlying diseases. One study found that patients with infections from resistant bacteria stayed an average of 9.5 days in an intensive care unit (ICU) while control patients stayed there 5 days (Ref. 9). The other study found that patients with infections from resistant bacteria stayed an average of 21 days in an ICU compared to 12.5 days for control patients (Ref. 10).

Three regional studies directly compared the costs of infections caused by resistant and susceptible bacteria. In the first study, using hospital discharge data from hospitals in New York City, researchers modeled differences between infections caused by MRSA and those caused by methicillin-susceptible *S. aureus* (MSSA). They estimated that each MRSA infection costs an additional \$2,500 in direct medical costs and longer hospital stays (Ref. 11).

The second study, performed at a university teaching hospital in North Carolina, also measured length of hospital stay and direct costs of hospitalization for patients with hospital-acquired bloodstream infections caused by MRSA and MSSA bacteria (Ref. 12). Patients infected with resistant bacteria stayed 8 additional days in the hospital (i.e., 12 days with MRSA infections compared to 4 days with MSSA infections), costing approximately \$17,000 more in direct hospital costs.

In the third study, conducted at a Boston hospital, researchers examined the economic impact of antibiotic resistance in *Pseudomonas aeruginosa* (Ref. 13). This study compared length of stay and costs for three groups: (1) Patients with susceptible bacteria, (2) patients with some baseline resistant bacteria, and (3) patients with resistance that emerged while hospitalized. Daily hospital charges of \$2,059 were the same for all three groups. Also, the

length of stay was similar for patients infected with susceptible bacteria and those with baseline resistant bacteria. However, patients in whom resistant bacteria emerged during hospitalization incurred additional costs of \$7,340 for 3.5 extra days.

The total number of annual infections caused by resistant bacteria is uncertain. Although diagnosis codes exist for infections with drug-resistant microorganisms, the codes are intended only to supplement other codes for infectious conditions and are not always included in patient data. As a result, hospital patient records may provide only an estimate of the minimum number of cases of drug-resistant infections in a given year. The U.S. National Center for Health Statistics publishes annual estimates of the number of diagnoses (by diagnosis code) in nonfederal short-stay hospitals from the National Hospital Discharge Survey (NHDS). NHDS estimates about 18,000 and 43,000 cases of infections by resistant microorganisms for 1995 and 1997, respectively (Refs. 14 and 15). On the basis of data from a larger national sample of hospital patients, the Healthcare Cost and Utilization Project (HCUP) estimates 84,000 diagnoses of resistant infections in community hospitals for 1997 (Ref. 16). CDC hospital surveillance data for 5 known strains of resistant bacteria for 1995 suggest a much higher figure, approximately 279,000 cases (Ref. 17). For this analysis, FDA has assumed the average of the 1995 data, or that 150,000 hospital-acquired infections per year are attributable to resistant bacteria. Thus, if patients incur additional hospital charges of only \$2,500 per resistant infection, the total hospital cost attributable to antibacterial resistance is estimated at \$375 million annually. However, these costs are likely understated because the more recent

products in the print version of the PDR are also included in the CD-ROM and Internet version.

⁷ \$842 per product = (\$9,500 per page + columns per page) x 0.266 column.

1997 studies found even greater costs and longer hospital stays associated with infections from resistant bacteria than the 1995 studies.

2. Indirect Costs of Resistant Infections

a. *Morbidity.* In addition to direct medical costs, patients also incur indirect costs from lost productivity due to resistant bacterial infections. FDA does not know how long a typical hospital stay is extended due to antibacterial resistance. However, if just 1 extra day were needed for relatively simple cases, at an average hourly wage of \$16 including benefits, each case would cost about \$128 in lost productivity. For cases where few alternatives are effective against the disease-causing bacteria, as with *Pseudomonas*, patients might need an additional 3.5 days in the hospital, with lost productivity cost of about \$448 per patient. Assuming the mean of these two estimates, 150,000 cases of resistant bacterial infections would cost the economy about \$43 million per year in lost productivity.

b. *Mortality.* The threat of mortality appears to be greater from hospital-acquired infections than from community-acquired infections. According to the CDC, about 40 percent

of all community-acquired infections from *S. pneumoniae* are penicillin-nonsusceptible (includes both intermediate-susceptible and resistant strains). These bacteria can cause infections such as bacteremia, pneumonia, meningitis, and otitis media. Until the mid-1990s, surveillance data for *S. pneumoniae* included few cases of resistant bacteria. Current surveillance data, however, show the incidence of resistant bacteria has dramatically increased, surpassing the incidence of intermediate-susceptible bacteria (Ref. 18). Several studies have reported higher crude mortality rates with infections caused by drug-resistant *S. pneumoniae* (DRSP) (Refs. 19, 20, 21, 22, and 23). However, once adjusted for age and severity of illness, mortality rates for patients with community-acquired infections from DRSP and drug-sensitive *S. pneumoniae* strains are statistically similar. As the incidence of community-acquired infections from resistant bacteria increases, the differences in mortality rates may become statistically significant.

In a report released last year, the World Health Organization estimated that 14,000 people die in the United

States annually from drug-resistant infections acquired in hospitals (Ref. 24). Several published studies have reported higher crude mortality rates from hospital-acquired infections caused by resistant bacteria. However, direct comparison of the findings of these studies is difficult because of differences in definitions, base line mortality rates, and the characteristics of patients included in the studies. In most studies, age and severity of illness confound the mortality data. Furthermore, because the prevalence of resistant bacteria is not uniform throughout the United States, studies conducted in a specific hospital or region may not be representative of the whole country.

To develop a rough estimate of the mortality that might be attributable to resistant bacterial infections, FDA estimated base line in-hospital mortality rates by age cohort, using hospital discharge and diagnosis data from HCUP (table 4 of this document). The number of life-years lost due to resistant bacterial infections was then derived from this base line mortality rate and from a weighted measure of the deaths attributable to resistant bacteria (27.1 percent).

TABLE 4.—1997 IN-HOSPITAL MORTALITY RATES BY AGE COHORT

Age cohort	Population (000) ¹	Number of In-Hospital Deaths ²	In-Hospital Mortality as % of Population for Age Cohort
Birth–17	69,603	25,739	0.04%
18–44	108,553	49,687	0.05%
45–64	55,441	143,670	0.26%
65–84	30,272	462,465	1.53%
85+	3,913	185,868	4.75%
Total	267,782	867,429	

¹ U.S. Department of Commerce, Census Bureau, Statistical Abstract of the United States: 2000, Table 12.

² 1997 hospital discharge data from HCUPnet, Healthcare Cost and Utilization Project, Agency for Healthcare Research and Quality (AHRQ), Rockville, MD, <http://www.ahrq.gov/data/hcup/hcupnet.htm>.

Table 5 of this document shows the number and monetary value of the life-years lost from resistant bacteria. The monetary values shown in columns 6 and 7 are derived by amortizing the value of a statistical life of \$5 million⁸

over the average remaining life span of a 35-year-old, which is estimated to be 44.3 years. At zero discount rate, this would be the equivalent of receiving a payment of \$112,867 per year. However, applying discount rates of 3 percent and

7 percent⁹, to reflect more plausible rates of social time preference, results in life-year values equal to \$205,493 and \$368,404, respectively.

⁸ The \$5 million estimate is the aggregate amount society is willing to pay to save one life. Fisher, A., D. Violette, and L. Chestnut, "The Value of Reducing Risks of Death: A Note on New Evidence," *Journal of Policy Analysis and Management*, vol. 8, pp. 88–100, 1989.

⁹ The Panel on Cost-Effectiveness in Health and Medicine convened by the U.S. Public Health Service recommends using a discount rate of 3 percent to calculate health benefits (Weinstein, M. C. et al. "Recommendations of the Panel on Cost-Effectiveness in Health and Medicine," *Journal of*

the American Medical Association, vol. 276, p. 1253–1258). OMB requires agencies to use a discount rate of 7 percent when calculating regulatory impacts.

TABLE 5.—ESTIMATED NUMBER AND MONETARY VALUE OF LIFE-YEARS LOST FROM DEATHS DUE TO INFECTIONS WITH DRUG-RESISTANT BACTERIA¹

Age cohort	Average Life Years Remaining for Each Cohort ²	Number of In-Hospital Diagnoses With Drug-Resistant Infections ^{3, 4}	Number of Deaths From Drug-Resistant Infections ⁵	Number of Life Years Lost From Drug-Resistant Infections	Monetary Value of Life Years Lost—3% Discount Rate (\$ Mil) ^{6, 7}	Monetary Value of Life Years Lost—7% Discount Rate (\$ Mil) ^{6, 8}
Birth—17	69.2	3,056	0.3	21.2	\$4.4	\$7.8
18—44	48.1	10,372	1.3	62.0	\$12.7	\$22.8
45—64	26.8	16,807	11.8	317.1	\$65.2	\$116.8
65—84	12.3	39,857	165.2	2,039.5	\$419.1	\$751.3
85+	4.2	13,838	178.4	750.6	\$154.2	\$276.5
Total		83,930	357.0	3,190.3	\$655.6	\$1,175.3

¹ Numbers may not sum or multiply due to rounding.

² Anderson, R. N., "United States Life Tables, 1997," *National Vital Statistics Reports*, vol. 47, Table 1, 1999.

³ 1997 hospital discharge data from HCUPnet, Healthcare Cost and Utilization Project, "AHRQ, Rockville, MD (<http://www.ahrq.gov/data/hcup/hcupnet.htm>).

⁴ Includes all reported ICD-9 V09 diagnoses (i.e., infection with drug-resistant microorganisms).

⁵ Baseline mortality from table 4 of this document. The number of deaths from drug-resistant infections was derived from published reports and HCUP data. Drug resistance increased mortality rates across all age cohorts by a weighted average of 27.1 percent. The mean percent increase in mortality rates and the estimated share of infections caused by the bacteria (shown in parentheses) are: 88 percent (5.3 percent) for vancomycin resistant *Enterococci* (Refs. 24, 25, 26, 27, 28, 29, 30, 31, 32, and 33); 103 percent (7.4 percent) for methicillin resistant *S. aureus* (Refs. 9, 10, 27, and 35); and 230 percent (6.5 percent) for *P. aeruginosa* (Refs. 12 and 36). No difference in mortality rates between resistant and susceptible strains was assumed for all other infection-causing bacteria. $27.1 \text{ percent} = (0.053 \times 0.88) + (0.074 \times 1.03) + (0.065 \times 2.30) + (0.808 \times 0)$ (may not sum or multiply to total because of rounding).

⁶ \$5 million = value of statistical life saved; 34.9 years = median age of population in 1997; 44.3 years remaining from 1997 Life Table, used to amortize \$5 million (see footnote 2 of this table).

⁷ \$205,493/life-year lost.

⁸ \$368,404/life-year lost.

3. Reduced Direct and Indirect Costs

Many factors can contribute to the development of antibiotic resistance, including the unnecessary use of antibiotics. The final rule adds statements to the professional labeling of these drugs that will encourage health care providers and patients to use antibiotics in a way that reduces the risk that antibiotic-resistant bacteria will develop, thus maintaining the effectiveness of these drugs.

As discussed elsewhere in this document, some comments to the agency questioned the effectiveness of labeling as an information tool. Health care organizations and government, however, can employ a variety of ways to inform stakeholders of the serious public health threat posed by resistant bacteria. Labeling that prompts health care providers and patients to use antibacterial drugs prudently will complement the educational efforts of organizations such as the AMA and CDC. The agency finds that while many health care providers infrequently consult the actual package insert, they often refer to the PDR for information about available drugs. Both the print and electronic versions of the PDR reproduce the professional labeling verbatim. Moreover, many patients use the PDR to obtain information about the drugs they are taking.

FDA cannot accurately quantify the magnitude of the impact that these changes in labeling will have on physician and patient behavior, or of its

subsequent impact on the development of resistant bacteria and their societal costs. If, however, the changes avoid even 1 percent of the above estimated costs of antibacterial resistance, the annual cost savings will amount to \$3.8 million in direct hospital costs, \$0.4 million in lost productivity, and from \$6.6 million to \$11.8 million in life-years lost (discounted at 3 percent and 7 percent respectively), for a total benefit exceeding \$10 to \$16 million annually.

If the costs of increased antibiotic resistance were decreased as little as 0.01 percent, the benefits of this rule would exceed the compliance costs estimated in the previous paragraph. FDA believes it is extremely likely that the decrease in the excess cost of antibiotic resistance will be at least this large, and is likely to be significantly larger.

D. Impacts on Small Entities

No comments on the initial regulatory flexibility analysis were received by the agency. The final rule affects manufacturers of systemic antibacterial drug products. The 1997 Economic Census found approximately 700 pharmaceutical preparation manufacturing firms in the United States (i.e., North American Industry Classification System (NAICS) code 325412). The Small Business Administration (SBA) considers firms with fewer than 750 employees to be small. As seen in table 6 of this document, Census data classify firms in

size categories that do not permit a precise determination of the number of pharmaceutical firms that have fewer than 750 employees. However, Census data do show that more than 90 percent of pharmaceutical manufacturers have fewer than 500 employees, and thus are small businesses (Ref. 12).

Approximately 101 large and small firms manufacture systemic antibacterial drug products¹⁰ and thus would be affected by the rule. The estimated annualized costs of \$861 per product¹¹ are relatively modest for most manufacturers of antibiotic drugs. Since small manufacturers of human prescription drugs already submit labeling to FDA, the labeling requirements of the rule will not require small firms to seek employees with additional special skills. As physicians and patients become more cautious in their use of antibiotics, some small antibiotic manufacturers could experience a decline in the demand for their products. The objective of the final rule is to safeguard the effectiveness of all antibiotic drug products. Thus, slowing the appearance of more resistant strains of bacteria will increase the demand for those antibiotic drugs that remain an effective treatment for those infections. More prudent use of

¹⁰ Derived from FDA's *Approved Drug Products With Therapeutic Equivalence Evaluations*, 2001, and *2001 Drug Information*, American Hospital Formulary Service.

¹¹ Total annualized costs per product: \$417,056 + \$24,439 + \$134,720 = \$576,216. Average annualized costs: \$576,216/669 = \$861.

antibiotics therefore will protect small, as well as large, manufacturers against the decline in demand that would otherwise follow a drop in product effectiveness.

Based on the previous analyses, any foreseeable significant adverse impacts of the rule would be incurred only by those small firms that manufacture many affected products and consequently would be required to change multiple package inserts at one time. We reviewed *FDA's Approved Drug Products With Therapeutic Equivalence Evaluations*, 2001, and identified only eight small domestic firms that manufacture more than three

antibiotic products. These 8 small firms manufacture 11, 8, 8, 6, 5, 4, 4 and 4 products respectively, 95 percent of which are generic products. At least 2 of the 3 firms with over 6 products are multi-million dollar firms with over 400 employees. Three of the eight firms also manufacture one reference listed drug product.

Table 6 of this document compares the estimated annualized and first-year costs of compliance to reported average annual sales revenues for pharmaceutical firms of varying sizes and for the average firm that primarily manufactures antimicrobial drugs. Almost all manufacturers of antibiotic

products in the United States have over 20 employees.¹² Thus, the last column of the table shows that the first-year costs will be less than two-tenths of one percent of sales revenues for almost all small firms. Based on the minimal impact implied by these data, FDA certifies that this final rule would not have a significant adverse economic effect on a substantial number of small entities.

¹² Derived from FDA's *Approved Drug Products With Therapeutic Equivalence Evaluations*, 2001, and *2001 Drug Information*, American Hospital Formulary Service.

TABLE 6.—EXAMPLES OF ANNUALIZED AND FIRST-YEAR COSTS TO MODIFY PROFESSIONAL LABELING AS A PERCENTAGE OF AVERAGE ANNUAL SHIPMENT VALUE BY NUMBER OF EMPLOYEES FOR NAICS 325412 AND 325412P¹

No. of Employees	No. of Establishments	Value of Shipments (mil\$)	Average Annual Per Establishment Shipment Value (mil\$)	Annualized Cost to Modify One Product as a Percentage of Shipment Value ²	Annualized Cost to Modify Two Products as a Percentage of Shipment Value ²	Annualized Cost to Modify Three Products as a Percentage of Shipment Value ²	First-Year Costs to Modify Three Products as a Percentage of Shipment Value ³
NAICS 325412 (All Pharmaceutical Preparation Manufacturing) Small Businesses By SBA Size Standards (fewer than 750 employees)							
1–4	179	90.0	0.5	0.17%	0.34%	0.51%	2.76%
5–9	88	137.5	1.6	0.06%	0.11%	0.17%	0.89%
10–19	128	451.6	3.5	0.02%	0.05%	0.07%	0.39%
20–49	138	1,078.4	7.8	0.01%	0.02%	0.03%	0.18%
50–99	85	2,486.1	29.2	0.00%	0.01%	0.01%	0.05%
100–249	107	7,846.8	73.3	0.00%	0.00%	0.00%	0.02%
250–499	62	15,217.1	245.4	0.00%	0.00%	0.00%	0.01%
500–999	29	13,720.8	473.1	0.00%	0.00%	0.00%	0.00%
Large Businesses by SBA Size Standards (750 or more employees)							
1,000–2,499	15	9,163.3	610.9	0.00%	0.00%	0.00%	0.00%
2500 +	6	17,328.5	2,888.1	0.00%	0.00%	0.00%	0.00%
NAICS 325412P (Primary Product Class = pharmaceutical preparations for human parasitic and infective diseases)							
All	28	6,480.3	231.4	0.00%	0.00%	0.00%	0.01%

¹U.S. Department of Commerce, Bureau of the Census, *Pharmaceutical Preparation Manufacturing: 1997 Economic Census of Manufacturing*, Industry Series, EC97M–3254B.

²Average annualized per product costs = \$861.

³Average first-year per product costs = \$4,616.

VI. Paperwork Reduction Act of 1995

FDA concludes that this final rule does not require information collections subject to review by OMB under the Paperwork Reduction Act of 1995 (the PRA) (Public Law 104-13). FDA received no comments on its determination concerning information collections.

FDA is amending its labeling regulations to require that the labeling for systemic antibacterial drug products include certain statements, specified by FDA, about the link between unnecessary use of antibiotics and the development of drug-resistant bacterial strains. These labeling statements are not subject to review by OMB because they are "originally supplied by the Federal Government to the recipient for the purpose of disclosure to the public" (5 CFR 1320.3(c)(2)) and therefore do not constitute a "collection of information" under the PRA of 1995.

Holders of approved new drug applications (NDAs) and abbreviated new drug applications (ANDAs) are required to submit supplements and holders of pending NDAs and ANDAs are required to submit amendments to comply with the new labeling requirements. The final rule also requires that all new NDAs and ANDAs for systemic antibacterial drug products comply with the new labeling requirements. FDA regulations governing the submission and approval of NDAs and ANDAs, including the submission of product labeling, are in part 314 (21 CFR part 314). Recordkeeping and reporting requirements included in part 314 are approved by OMB until March 31, 2005, under OMB control number 0910-0001.

VII. Federalism

FDA has analyzed this final rule in accordance with the principles set forth in Executive Order 13132. FDA has determined that the rule does not contain policies that have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, the agency has concluded that the rule does not contain policies that have federalism implications as defined in the Executive order and, consequently, a federalism summary impact statement is not required.

VIII. References

The following references have been placed on display in the Dockets Management Branch (see ADDRESSES)

and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

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List of Subjects in 21 CFR Part 201

Drugs, Labeling, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 201 is amended as follows:

PART 201—LABELING

1. The authority citation for 21 CFR part 201 continues to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 358, 360, 360b, 360gg-360ss, 371, 374, 379e; 42 U.S.C. 216, 241, 262, 264.

2. Add § 201.24 to subpart A to read as follows:

§ 201.24 Labeling for systemic antibacterial drug products.

The labeling of all systemic drug products intended for human use indicated to treat a bacterial infection, except a mycobacterial infection, must bear the following statements:

(a) At the beginning of the label, under the product name, the labeling must state:

To reduce the development of drug-resistant bacteria and maintain the effectiveness of (*insert name of antibacterial drug product*) and other antibacterial drugs, (*insert name of antibacterial drug product*) should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

(b) In the "Indications and Usage" section, the labeling must state:

To reduce the development of drug-resistant bacteria and maintain the effectiveness of (*insert name of antibacterial drug product*) and other antibacterial drugs, (*insert name of antibacterial drug product*) should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

(c) In the "Precautions" section, under the "General" subsection, the labeling must state:

Prescribing (*insert name of antibacterial drug product*) in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

(d) In the "Precautions" section, under the "Information for Patients" subsection, the labeling must state:

Patients should be counseled that antibacterial drugs including (*insert name of antibacterial drug product*) should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When (*insert name of 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. 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 (*insert name of antibacterial drug product*) or other antibacterial drugs in the future.

Dated: October 4, 2002.

Mark B. McClellan,

Commissioner of Food and Drugs.

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DEPARTMENT OF THE TREASURY

Internal Revenue Service

26 CFR Part 1

[TD 9022]

RIN 1545-BB40

Information Reporting Relating to Taxable Stock Transactions; Correction

AGENCY: Internal Revenue Service (IRS), Treasury.

ACTION: Correction to temporary regulations.

SUMMARY: This document contains corrections to temporary regulations

that were published in the **Federal Register** on November 18, 2002 (67 FR 69468). This document contains temporary regulations under section 6043(c) requiring information reporting by a corporation if control of the corporation is acquired or if the corporation has a recapitalization or other substantial change in capital structure.

DATES: This correction is effective November 18, 2002.

FOR FURTHER INFORMATION CONTACT: Nancy Rose at (202) 622-4910 (not a toll-free number).

SUPPLEMENTARY INFORMATION:

Background

The temporary regulations that are the subject of this correction are under section 6043(c) of the Internal Revenue Code.

Need for Correction

As published, the temporary regulations (TD 9022) contains errors that may prove to be misleading and are in need of clarification.

Correction of Publication

Accordingly, the publication of the temporary regulations (TD 9022), which is the subject of FR Doc. 02-29199, is corrected as follows:

1. On page 69469, column 2, in the preamble, under the paragraph heading "Background and Explanation of Provisions", line 5, the language "regulations published in proposed rules" is corrected to read "regulations published in the proposed rules".

§ 1.6043-4T [Corrected]

2. On page 69470, column 1, § 1.6043-4T, paragraph (a)(5), the last line in column one, the language "shareholders who receive cash, stock or" is corrected to read "shareholders who receive cash, stock, or".

3. On page 69472, column 1, § 1.6043-4T, paragraph (h), of *Example 2*, line 1, the language "Example 2. C, a domestic corporation, and" is corrected to read "Example 2. C, a domestic corporation and".

§ 1.6045-3T [Corrected]

4. On page 69473, column 1, § 1.6045-3T, paragraph (d), line 2, the language "receives stock, cash or other property" is corrected to read "receives stock, cash, or other property".

Cynthia E. Grigsby,

Chief, Regulations Unit, Associate Chief Counsel, (Procedure and Administration).

[FR Doc. 03-2802 Filed 2-5-03; 8:45 am]

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