

*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